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DISEASES

of the

CHEST

OFFICIAL PUBLICATION



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1. Nussbaum, H. E., Leff, W. A., Mattia, V. D., Jr. and Hillman, E.: An effective combination in the treatment of the hypertensive patient. *Am. J. M. Sc.* 234: 150, Aug. 1957.

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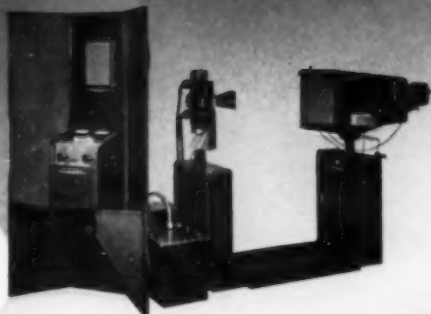
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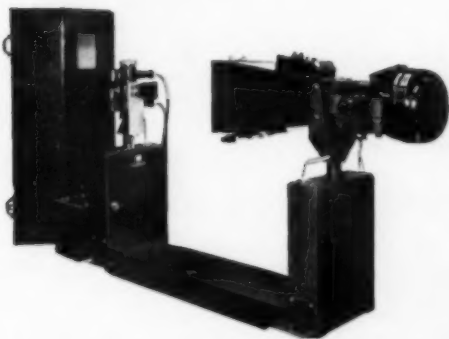
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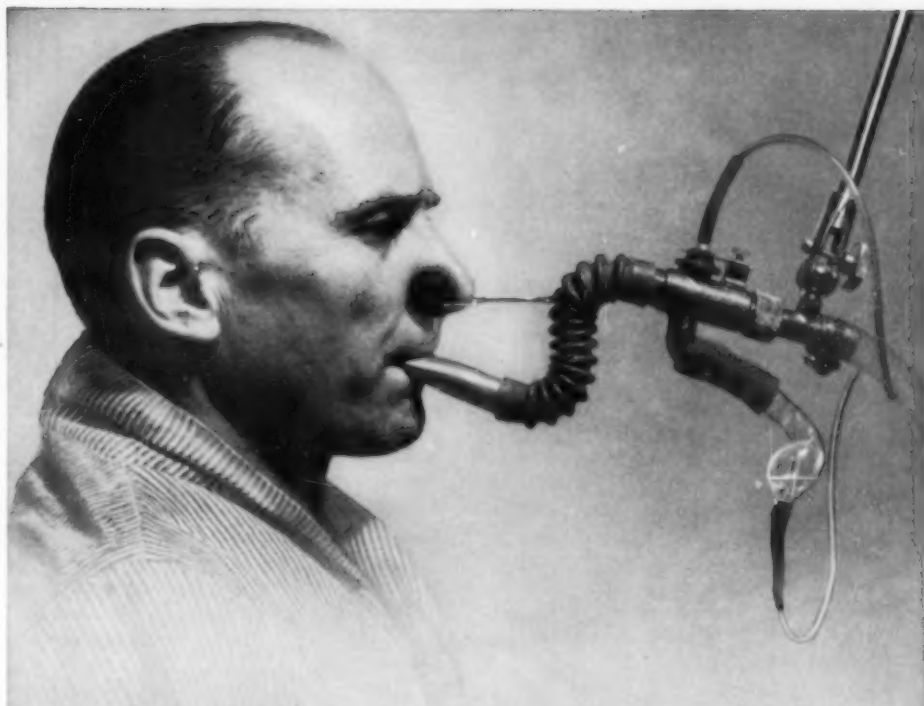
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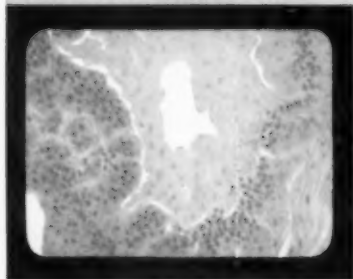
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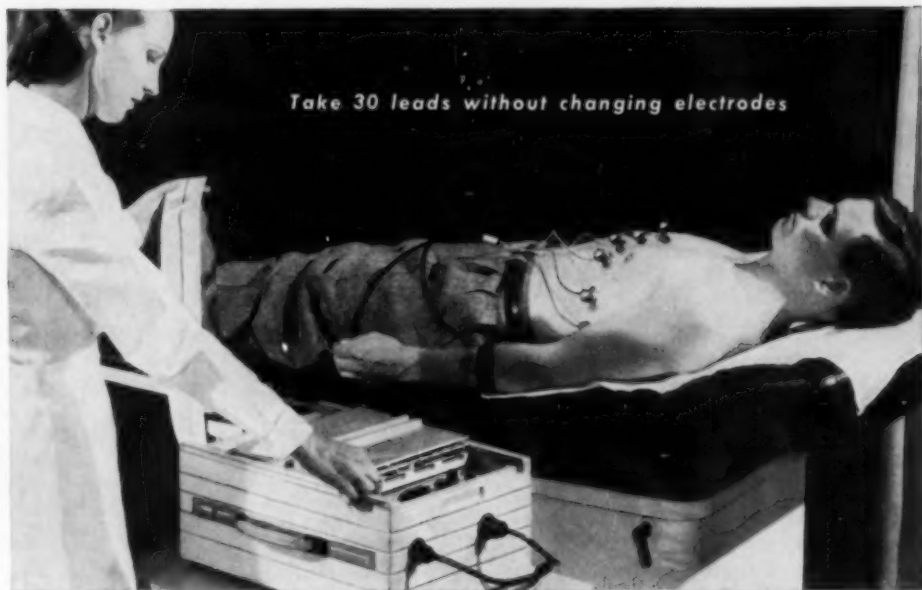
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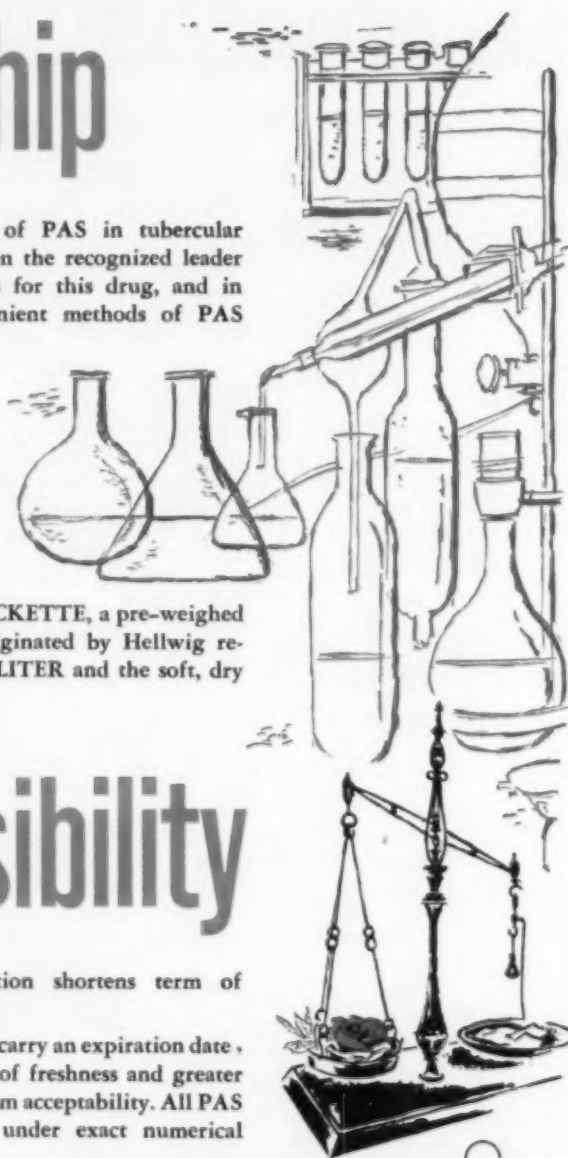
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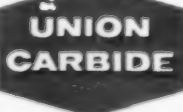
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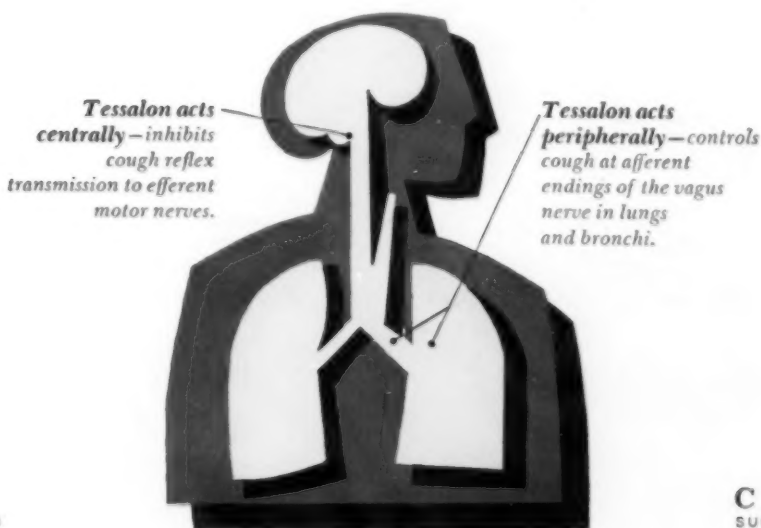
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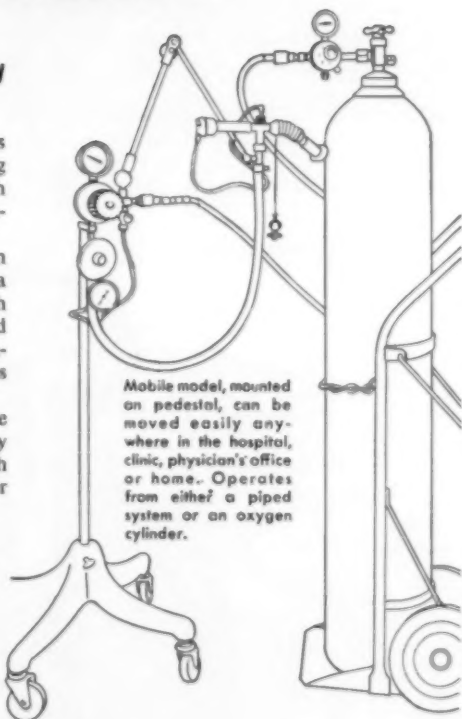
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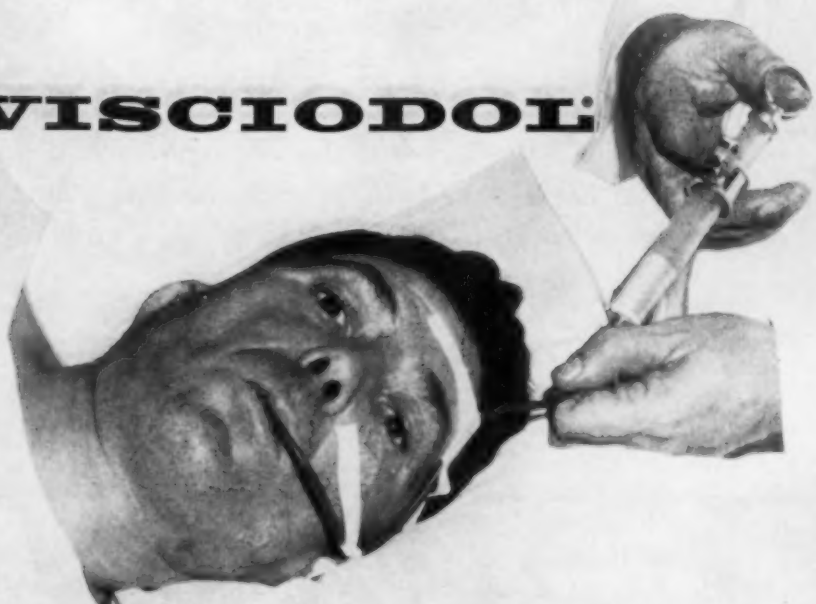
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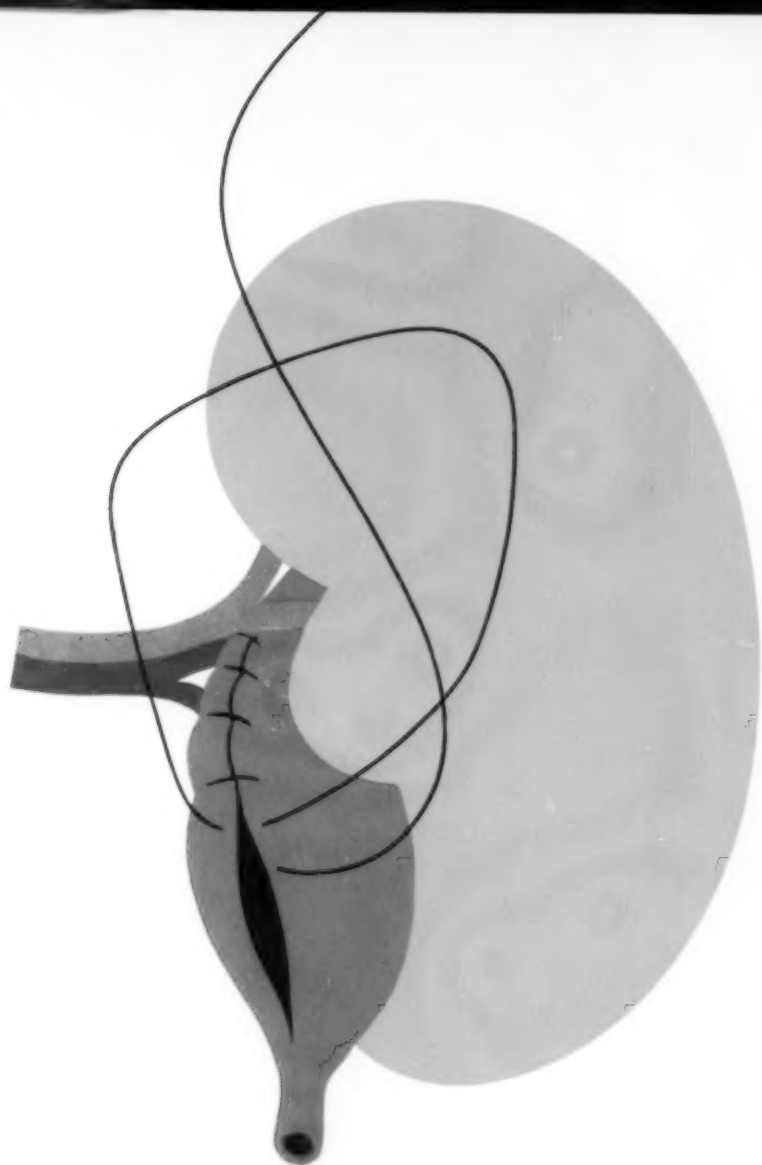
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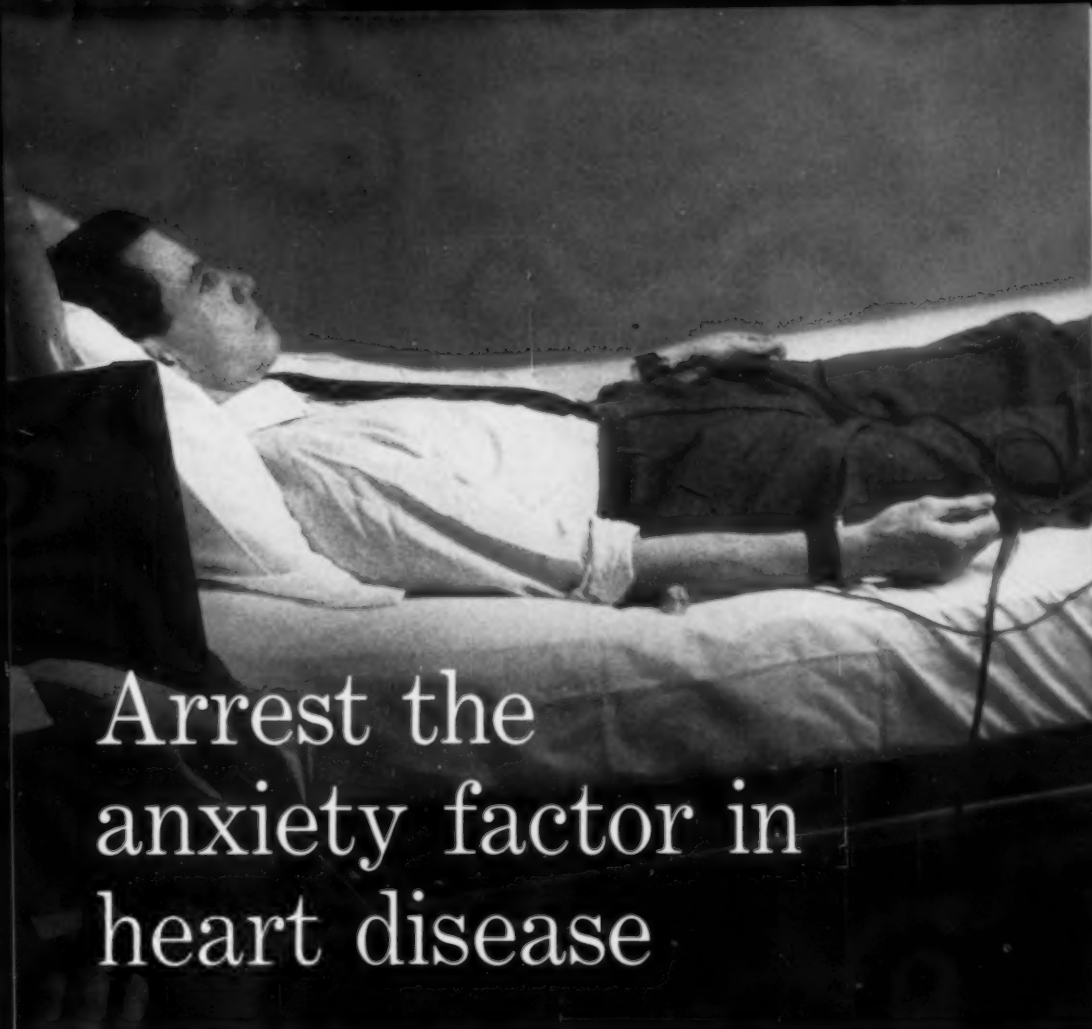


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*Waldman, S. and Peiner, L.: Management of anxiety associated with heart disease. *Am. Pract. & Digest Treat.* 8:1075, July 1957.

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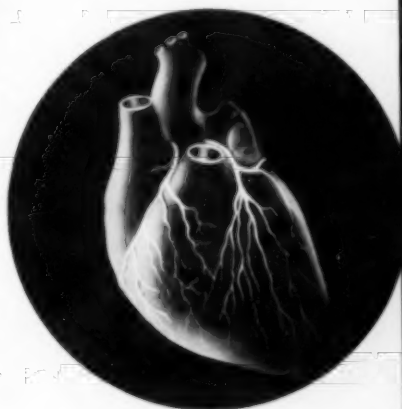
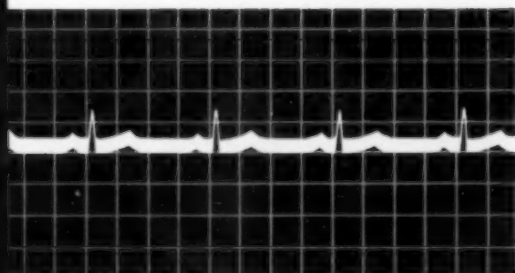
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1. Molthan, L., Cohen, R.V., and Zarafonitis, C.J.D.: *Am. Rev. Tuberc.* 71:220, 1955.

2. Cohen, R.V., Molthan, L., and Zarafonitis, C.J.D.: *Dis. Chest* 30:418, 1956.

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1. Aravanis, C., and Luisada, A. A.: Am. J. Cardiology, in press.

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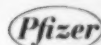
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References: 1. Shubin, H., and Heiken, C. A.; Antibiotics Annual 1955-1956, New York, Medical Encyclopedia, Inc., 1956, p. 173. 2. Ross, J. D.; Horne N. W.; Grant, W. B., and Crofton, J. W.; Brit. M. J. 1:5065 (Feb. 1) 1956.
3. Kass, I.; Russell, W. F., Jr.; Heaton, A.; Miyamoto, T.; Middlebrook, G., and Dressler, S. H.; Ann. Int. Med. 47:744 (Oct.) 1957.
4. Feldmann, F. M., Medical Director, National Tuberculosis Association; Pediatrics 21:319 (Feb.) 1958.

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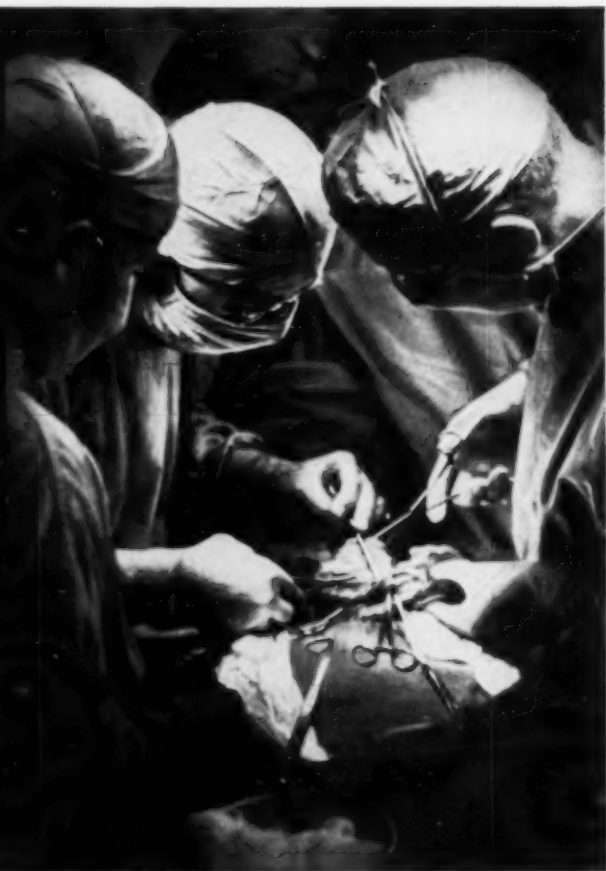
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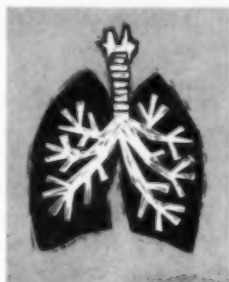
⁽¹⁾CLORPACTIN. A Surgical Adjunct: Antimicrobial and Tumoricidal Properties; Gledman, M., Grant, R., Vestal, B., Rogers, C., Karlson, K. E. Presented at the Surgical Forum of the American College of Surgeons October 17, 1957.

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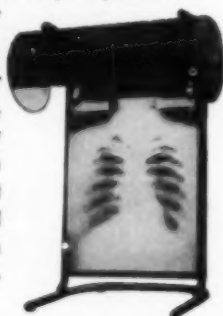
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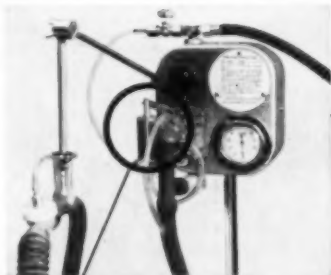
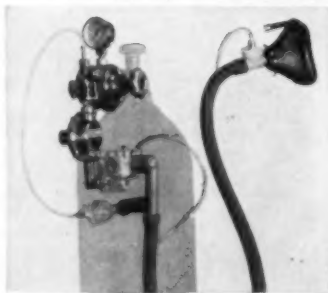
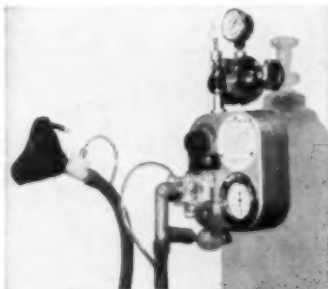
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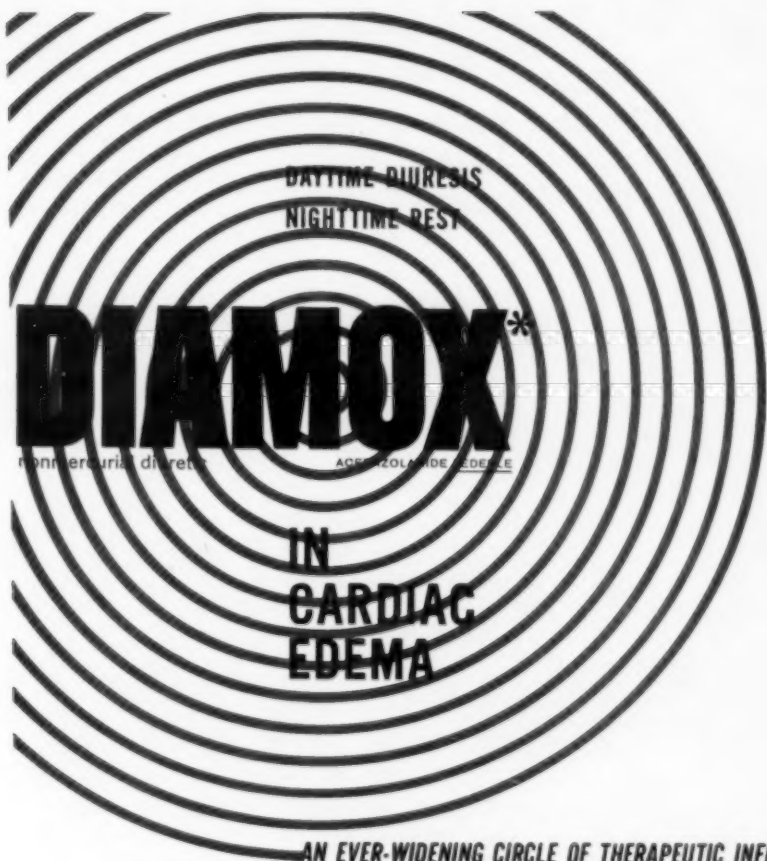
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¹Braveman, W. S.; Dexter, R. S., and Rubin, A. L.: Diamox (Acetazolamide) as an Oral Diuretic in Ambulatory Cardiac Patients. *Am. Heart J.* 54:284-290, 1957.

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VOLUME XXXIII

JUNE, 1958

NUMBER 6

Studies on the Nature of the Arterial Blood Oxygen Unsaturations in Chronic Pulmonary Disease^{*,**}

HURLEY L. MOTLEY, M.D., F.C.C.P.†

Los Angeles, California

Hypoxemia (anoxemia) occurs when there is interference in the transfer of oxygen from the alveoli to the blood in the capillaries. Hypoxemia may be present although alveolar ventilation is normal. Oxygen diffuses across the pulmonary membrane to combine with hemoglobin (oxyhemoglobin) in the capillaries because there is a difference in partial pressure of oxygen (pO_2) in the two compartments. The oxygen molecules move from a region of higher concentration to a region of lower concentration (diffusion). The pulmonary membrane includes everything through which oxygen must diffuse from the alveolus to combine with the hemoglobin in the red blood cell, namely: alveolar membrane; interstitial fluid between alveolar and capillary membrane; capillary membrane; plasma and outer membrane layer of the red blood cell.

In recent years there has been a revival of studies of measurements of the diffusing capacity of the lung.¹⁻³ The diffusing capacity of the lung is defined as the quantity of a gas (oxygen or carbon monoxide) transferred each minute for each millimeter of mercury difference in partial pressure of the gas across the alveolar capillary membrane (normal for oxygen greater than 15 at rest). The diffusing capacity is concerned with all factors affecting the diffusion of gases between the alveoli and the pulmonary capillary blood. A decrease in the pulmonary blood flow as a result of a reduced number of patent capillaries or a decrease in the number of capillaries in contact with functioning alveoli decreases diffusion capacity, as well as an increased resistance at the pulmonary membrane for oxygen diffusion. Present tests for diffusion capacity measure the rate of diffusion and local variation with alveolar ventilation and volume (over ventilated alveoli) make difficult the definition and determination of the over-all pulmonary diffusing capacity.

A number of papers have been published in which the term alveolar-capillary membrane block has been used almost synonymously with decreased diffusion capacity of the lung, indicating the defect responsible for unsaturation as being specifically in the alveolar-capillary membrane.

*This investigation was supported in part by Research Grant H-1606 (C3), National Institute of Health, U. S. Public Health Service.

**Presented at the 23rd Annual Meeting, American College of Chest Physicians, New York City, May 29-June 2, 1957.

†From the Cardio-Respiratory Laboratory, University of Southern California School of Medicine.

Some have assumed that in all cases with fibrosis where emphysema is not a problem and the carbon dioxide is being blown off adequately, that the lowering of the arterial blood oxygen saturation is due to an alveolar-capillary membrane block, and this was even diagnosed from the chest roentgenogram.⁴ The term "alveolar-capillary block" has been described as a specific defect in diffusion for oxygen across the pulmonary membrane, where an increased difference between the mean alveolar and mean capillary pO_2 exists, with a resulting lowering in the arterial blood oxygen saturation especially with exercise. Breathing a high oxygen mixture should overcome the block and restore the saturation to normal. Most of the papers reporting measurements on the so-called alveolar-capillary membrane block use 100 per cent oxygen at rest, and if the saturation is 99 to 100 per cent, a diffusion difficulty at the pulmonary membrane is stated to exist. Emphysema and carbon dioxide retention are frequently not present in a significant degree in the presence of severe hypoxia at rest, and more often with exercise, in pulmonary fibrosis, sarcoidosis, the collagen group of diseases and the pneumoconioses. The purpose of this paper is to present data showing that in most cases of pulmonary fibrosis and other pulmonary conditions as listed above, with exception of berylliosis, that the principal cause of the lowering of the arterial blood oxygen saturation is not due to an alveolar-capillary membrane block. The hypoxia is due to perfusion of blood through nonventilated areas especially at the alveolar level and to the presence of poorly ventilated alveoli. The basic consideration in studying the specific cause for unsaturation is based on two simple tests to be described.

Wilson et al⁵ report the ratio of the average cross-sectional area involved in diffusion to thickness of the respiratory membranes as 15-31 meters per micron. The surface area of the respiratory alveoli has been estimated, if flattened out, to be from 75 to 100 square meters in man (about the size of a tennis court). By virtue of the large surface area of exposure the passage of the red blood cell through the pulmonary capillaries affords maximal diffusion area for the oxygen to contact the hemoglobin. The thin pulmonary capillaries have been described as virtually hanging in space, thus providing a maximal surface area contact for gas exchange, especially oxygen with the hemoglobin as the red blood cells flow by in single file. The pulmonary bed provides very little tissue support of the capillaries, with most of the gas exchange surface of the vessels exposed to atmospheric pressure. The intimate contact of oxygen and hemoglobin as provided by the alveolar surface area is necessary if all the hemoglobin is to be converted to oxyhemoglobin, for once beyond the capillaries the piling up of red blood cells (4,000,000 to 5,000,000 per cubic millimeter) offers a mechanical barrier to full saturation of all the hemoglobin, even though the oxygen tension of the plasma be adequate or even elevated.

The principle of the large surface area for contact between oxygen and hemoglobin in order to get all of the hemoglobin combined as oxyhemoglobin is employed in measuring oxygen capacity by the Van Slyke method,

where a given volume of blood is placed in a proper sized flask, and the flask rotated on the side for 25 minutes (for example, 3 cc. of blood in a 25 cc. Erlenmeyer flask). The thin film of blood affords maximal opportunity for all the hemoglobin to be combined as oxyhemoglobin from the oxygen in the air in the flask. If too much blood be added to a given sized flask (for example, 6 cc. of blood in a 25 cc. flask), the film of blood will be too thick for all of the hemoglobin to be combined as oxyhemoglobin on exposure to air, so that some of the hemoglobin is not converted to oxyhemoglobin by exposure to air in the flask even after 25 minutes (the thickness of the film here being a physical factor impairing the completeness of the reaction). In order for the hemoglobin to be normally oxygenated in the transit through the pulmonary capillary network, the oxygen pressure in the capillary blood (dependent on the alveolar capillary partial pressure of oxygen) must be high while the cells are spread out during passage through the capillaries (time average usually less than 1.0 second).

The measurement of the blood gases in a sample of arterial blood from a systemic vessel such as the brachial artery reflects changes occurring in the lung and in conjunction with analysis of the expired air permits an evaluation of the type of changes which may be present. The saturation of the hemoglobin with oxygen is normally 96 to 98 per cent at sea level on air breathing, both at rest and with exercise, and the slight reduction results from venous admixture in the passage of the blood through the lungs and heart. The normal arterial partial pressure of oxygen (pO_2) is 95 mm. Hg. as measured by direct tension with the Riley⁶ bubble method. The mean alveolar pO_2 can be calculated from the arterial pO_2 , the arterial pCO_2 and the R.Q. of the expired air. Wilson et al⁵ report the normal average oxygen tension in the capillaries as 4 mm. Hg. less than in the pulmonary alveoli, and that 0.01 of the blood flow through the lung normally does not perfuse oxygenating capillaries. For all practical clinical considerations the arterial pCO_2 and the alveolar pCO_2 are the same (CO_2 is about 25 times as diffusible as oxygen in solution). If the arterial blood is unsaturated while breathing air at sea level, the arterial pO_2 is decreased, less than 95 mm. Hg. with a pH of 7.40. The decrease may be due to a lowered oxygen gas tension in the alveoli in all or in part due to inequalities of ventilation. The oxygen tension can be no higher in the blood than in the alveoli perfused as far as known in man, although the possibility of countercurrents as demonstrated in fish gills and swim bladder and in the placenta of many animal species may later be shown to be a factor, especially in conditions with chronically altered hemodynamics and possible extensive collateral circulation between the bronchial and pulmonary vessels. When the mean alveolar pO_2 is normal, a decrease in the arterial blood oxygen saturation as measured from a sample obtained from the brachial artery is due to: (1) a diffusion difficulty at the alveolar-capillary membrane (alveolar-capillary block), (2) shunting of blood through nonventilated areas either in the lung or in the heart, or (3) to poorly ventilated alveoli or nonventilated alveoli.⁷

The blood flow through the lung takes the path of least resistance and apparently selective diversion of the flow of blood occurs in regions with high vascular resistance to areas with less resistance. Many patients with extensive lung disease as revealed by the chest roentgenogram, have surprisingly good arterial blood oxygen saturation at rest, as the blood flow is diverted to the better ventilated and perfused areas. However, with mild exercise gross abnormalities in saturation may be revealed with the increased cardiac output and the loss of the selective diversion of flow. In the evaluation of the blood gas exchange the exercise measurements are frequently of greater importance than the resting measurements.⁷ Rest and exercise represent two different hemodynamic situations even in the same individual and studies on both aspects are necessary to obtain the essential information. Some cases, which have 100 per cent saturation at rest on 100 per cent oxygen breathing, will not have 100 per cent saturation if this test were repeated with exercise.

The simple test of using different levels of high oxygen breathing helps to differentiate a true diffusion difficulty (alveolar-capillary membrane block) from shunting at the alveolar level produced by very poorly ventilated alveoli or nonventilated alveoli, whereas 100 per cent oxygen breathing tends to obscure multiple small areas of shunting at the alveolar level because of the very high partial pressure of the dissolved oxygen in the plasma which perfuses ventilated alveoli in the smaller venules before the red blood cells become so piled up as in the larger vessels of a big arteriovenous fistula. A 32 per cent oxygen breathing mixture increases the inspired oxygen tension over 70 mm. Hg., and this is a large enough margin to overcome a diffusion difficulty at the alveolar-capillary membrane if that be the significant or primary difficulty in producing the unsaturation on air breathing. On the other hand, if the decrease in the saturation be due to shunting at the alveolar level, the arterial saturation will not be normal predicted for a 32 per cent oxygen breathing gas, as the increase in the oxygen partial pressure in the plasma will not obscure the shunting at the alveolar level as in the case of 100 per cent oxygen breathing. In some cases even 40 per cent oxygen does not elevate the saturation to the normal level with exercise when the difficulty is due to shunting at the alveolar level. In many cases the arterial blood oxygen saturation is decreased only in a slight to moderate degree at rest, but with mild exercise there is a marked drop in the saturation even though emphysema is not a factor and the maximal breathing capacity is fairly good. Total lung capacity is frequently very markedly decreased in these cases, yet the carbon dioxide may be normal. The decrease in total lung capacity may be due to pulmonary fibrosis, sarcoidosis, asbestosis, collagen type diseases, such as lupus erythematosus and pneumoconiosis.

A second simple test employed in determining the nature of the arterial blood oxygen unsaturation is the use of intermittent positive pressure breathing with compressed air only (no bronchodilators).⁸ The intermittent positive pressure breathing (IPPB) produces an increased tidal volume in most cases with some degree of hyperventilation. The increase

in mean pressure for the entire breathing cycle is usually less than 5 mm. Hg., when the peak cycling pressure is set at 20 cm. water. If a significant increase in the arterial blood saturation occurs with the pressure breathing on air, the only way to explain this finding is on a basis of providing improved aeration for poorly ventilated alveoli. The pressure breathing at rest on air does not elevate the inspired pO_2 to a sufficient degree to be a factor in overcoming a diffusion difficulty if that be a significant factor present at the alveolar-capillary membrane. Pressure breathing produces no significant change in the resting arterial blood oxygen saturation in cases with proven shunts from right to left in the lung, such as arterio-venous fistula. The improved saturation with pressure breathing on compressed air indicates the presence of poorly ventilated alveoli on ambient air breathing. In some cases an increase was noted in the arterial blood oxygen saturation during mild exercise. This is comparable to that produced by intermittent positive pressure breathing on compressed air only, and represents a more uniform alveolar aeration provided by the deeper breathing with exercise and the increased tidal volume.

Studies of the nitrogen washout employing the nitrogen meter and continuous recording of each breath during 100* per cent oxygen breathing has revealed, especially in severe pulmonary emphysema, marked obstruction at the parenchyma level. In some cases, more than 15 minutes of 100 per cent oxygen breathing are required to reduce the end tidal nitrogen to one per cent, and even then with a forced exhalation, the alveolar

*The oxygen tanks actually contained 0.3 to 0.5 per cent nitrogen by gas analysis.

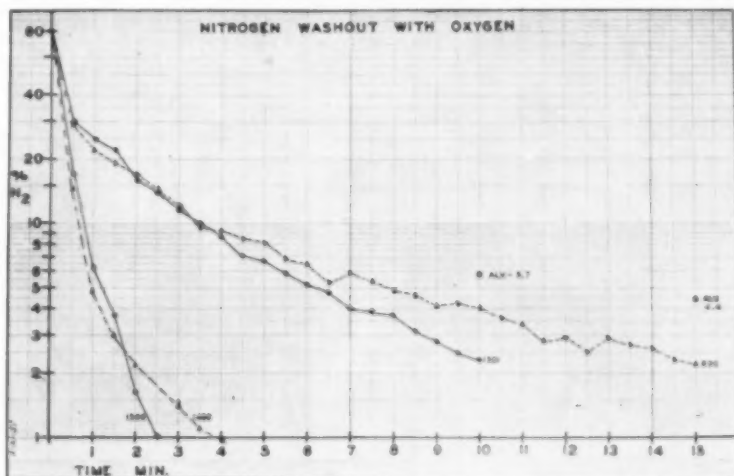


FIGURE 1: Nitrogen washout with oxygen breathing with the Waters Nitrogen Meter in two normals (No. 1500 and No. 1499) and in two patients with severe pulmonary emphysema (No. 1501 and No. 800). In Case 1501 the end tidal nitrogen was 2.3 per cent and the alveolar 5.7 per cent after 10 minutes of oxygen breathing. In Case 800 the end tidal was 2.2 per cent nitrogen with an alveolar of 4.4 per cent nitrogen after 15 minutes of oxygen breathing. This indicates obstruction in the smallest bronchioles in the parenchyma and markedly interferes with the uniformity of alveolar aeration.

TABLE I.—Studies on the Nature of the Arterial Blood Oxygen Unsaturations in Pulmonary Disease

| Case Number | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|--|---|---|---|------------------------------------|----------|----------|-------------|------------------------------|------------|-----------------------------|------------------------|
| Diagnosis | Largely, AV Fistula, Left Lower Lobe | Multiple, Large A-V Fistula All Lobes | Multiple, Small A-V Fistula All Lobes | Atrial Septal Defect, Pulmo- nary Hyper- tension | Bronchiectasis and Emphysema | Fibrosis | Fibrosis | Sarcoidosis | Lupus Erythe- matosus (?) | Asbestosis | Diatomite Pneumocystosis | Pulmonary Emphysema |
| Age, years, M (Male) F (Female) | 22 (M) | 40 (F) | 30 (F) | 32 (M) | 55 (F) | 66 (M) | 37 (F) | 32 (F) | 22 (M) | 58 (M) | 65 (M) | 57 (M) |
| Body Surface Area, Sq. M. | 1.69 | 1.59 | 1.79 | 1.70 | 1.62 | 1.96 | 1.59 | 1.44 | 1.93 | 1.60 | 1.65 | 1.66 |
| Total Vital Capacity, Per Cent Predicted | 79.0 | 120.3 | 105.0 | 66.7 | 60.8 | 60.2 | 47.7 | 35.6 | 15.6 | 69.5 | 100.0 | 59.3 |
| Timed Vital Capacity, 3 sec. Per Cent Predicted | 79.0 | 112.1 | 98.1 | 58.3 | 45.9 | 60.2 | 47.7 | 34.2 | 15.6 | 56.8 | 82.8 | 33.6 |
| Maximal Breathing Capacity, Per Cent Predicted | 98.0 | 123.0 | 87.1 | 66.0 | 63.6 | 107.3 | 89.8 | 75.9 | 35.4 | 73.7 | 95.7 | 21.5 |
| Residual Air Per Cent Predicted | 85.7 | 116.0 | 89.6 | 112.3 | 158.8 | 40.6 | 68.9 | 57.1 | 65.0 | 126.1 | 132.6 | 304.9 |
| Total Lung Capacity, Per Cent Predicted | 80.0 | 115.5 | 98.4 | 72.3 | 81.7 | 55.7 | 50.0 | 40.7 | 24.7 | 74.1 | 109.8 | 120.7 |
| Residual Per Cent Total Lung Capacity | 21.0 | 25.1 | 18.2 | 31.1 | 48.7 | 21.9 | 34.5 | 28.0 | 52.6 | 42.5 | 36.2 | 63.2 |
| Ventilation Factor, Per Cent | 90.2 | 111.6 | 98.3 | 62.9 | 53.6 | 95.8 | 70.0 | 60.5 | 29.7 | 63.1 | 87.1 | 31.6 |
| Arterial Blood Oxygen Saturation Per Cent | 89.0 | 64.8 | 87.6 | 85.3 | 92.7 | 93.8 | 96.0 | 87.8 | 76.1 | 93.8 | 92.5 | 85.2 |
| Rest, IPPB Air | | | 87.5 | 84.5 | 96.0 | 96.4 | | 92.0 | | 96.5 | 93.5 | 92.0 |
| Rest, 32 Per Cent O ₂ | | | | | | | | | 95.8 | | | 94.2 |
| Rest, 40 Per Cent O ₂ | | 69.0 | 92.4 | 86.5 | | | | | | | | |
| Rest, 100 Per Cent O ₂ | 90.6 | 75.5 | 97.2 | 94.4 | 98.9 | 99.8 | 99.0 | 99.0 | 99.1 | 99.6 | 95.8 | 97.0 |

nitrogen is elevated, Fig. 1. Such severe obstruction markedly impairs the ventilation of many alveoli and results in a lowering of the partial pressure of oxygen in the poorly ventilated alveoli, and in turn the saturation of the hemoglobin in the capillaries perfusing these areas.

The data from the 12 cases presented in Table I illustrate a variety of clinical conditions which show alterations in the arterial blood oxygen saturation both at rest and with exercise (one minute step-up test of 30 steps on an 8-inch stool). Intermittent positive pressure breathing with compressed air only and graded levels of oxygen breathing (32 per cent oxygen and 40 per cent oxygen) as well as 100 per cent oxygen breathing have been compared both at rest and with exercise for the effect on the arterial blood oxygen saturation. A breathing mixture of 32 per cent or 40 per cent oxygen does not obscure shunting at the alveolar level whereas 100 per cent oxygen may obscure shunting at the alveolar level especially at rest. However, with exercise due to alterations in perfusion-ventilation relationships the hemodynamic situation is different from that at rest so that the selective perfusion of blood through the better ventilated areas, which may be present at rest, no longer holds, because the increased cardiac output produces perfusion through more poorly ventilated or nonventilated areas. A 32 per cent oxygen breathing mixture increases the inspired pO_2 over 70 mm. Hg. and this is adequate to more than overcome an alveolar-capillary membrane block which might be present, for if the block were of greater magnitude than this value (alveolar-arterial pO_2 difference of 70 mm. Hg.) the patient would be unable to live on air breathing. The use of a 40 per cent oxygen breathing mixture almost doubles the inspired pO_2 as compared to air breathing. It can be noted that the resting arterial blood oxygen saturation on 100 per cent oxygen in all of the cases except those with large shunts and those with emphysema had a saturation of around 99 per cent or more, Table I. However, the exercise saturation on 100 per cent oxygen may not be normal, even though the saturation is normal at rest. The cases presented in Table I are type cases and illustrate the consistent findings observed in this laboratory in differentiating the nature of the arterial blood oxygen unsaturation. The arterial blood oxygen saturation was determined on the Van Slyke with duplicate checks on two different machines by different technicians. The arterial blood oxygen saturation per cent was also determined on the Water's oximeter double scale cuvette with the use of whole blood. The oximeter was checked daily against the Van Slyke (when properly calibrated, checks consistently within one per cent). Hemoglobin was determined from the flask capacity, direct Van Slyke capacity and the Beckman D-U Model Spectrophotometer using the cyanmethemoglobin method.¹⁰

In the presence of a large shunt such as an arterial venous fistula in one lobe of the lung (localized in the left lower lobe, by pulmonary angiograms), even 100 per cent oxygen breathing at rest does not produce a normal saturation as shown in Case 1, Table I. In this case there was a very high alveolar-arterial pO_2 difference of 63 mm. Hg. at rest. Ventilation was adequate, emphysema was not a factor, and carbon dioxide

was decreased. Studies on this case following a left lower lobe lobectomy revealed the restoration of the normal arterial blood oxygen saturation, 97.5 per cent at rest, 96.3 per cent with exercise and 100 per cent on oxygen breathing. Removal of the large shunt restored to normal the blood gas exchange.

In the presence of multiple large arteriovenous fistulae (pulmonary angiograms showed all lobes involved), the degree of unsaturation was very marked, even on high oxygen breathing mixture, as shown in Case 2 (75.5 per cent at rest on 100 per cent oxygen breathing). The exercise saturation was still lower both with air breathing and on 100 per cent oxygen breathing, Table I. Ventilation was not a factor as alveolar ventilation was increased, and carbon dioxide was blown off at a greater rate than normal as shown by the marked lowering in the arterial CO_2 content and pCO_2 (by direct tension measurements). The alveolar-arterial pO_2 difference was markedly increased 65 mm. Hg. Hyperventilation is a prominent feature in this type of case (a compensatory mechanism to increase as much as possible the arterial pO_2) and decreases the effective tidal air. High oxygen breathing does not correct the saturation to normal at rest in large shunts in the lung of which this is a diagnostic feature.

In the presence of multiple small arterio-venous fistulae in all lobes of the lung, Case 3, the resting saturation on air breathing was considerably higher than noted in the large fistulae in Case 2. The diagnosis in Case 3 was in some doubt not being fully established until after death. Some clinicians doubted the physiological diagnosis of arteriovenous fistula, since (1) pulmonary angiograms were read as negative, (2) a lung biopsy had failed to reveal a fistula and (3) they thought the arterial blood oxygen saturation on oxygen breathing at rest (97.2 per cent) too high for multiple shunts in the lung. Cardiac catheterization revealed a normal pulmonary artery pressure and no evidence of intracardiac shunting from right to left. On 40 per cent oxygen breathing the saturation was only 92.4 per cent, and this can only mean one thing, perfusion of blood through nonventilated areas. An alveolar-capillary membrane block which would produce a 92.4 per cent saturation on 40 per cent oxygen breathing would be inconsistent both with life on air breathing and with the 87.5 per cent saturation obtained on air breathing on rest. The ventilation measurements were good, emphysema was not a factor, and carbon dioxide was decreased as shown by the arterial CO_2 content and pCO_2 by direct tension measurements. Plastic injection of one lung after death revealed multiple small arterio-venous fistulae (actually several mm. in diameter) after the technic of Liebow.¹¹ Even at the postmortem examination the presence of multiple small arterio-venous fistulae was doubted by the pathologist. The shunting here is at a much smaller level for vessel size as compared to Case 2, but at a much larger level of vessel size (cross section area) as compared to shunting at the alveolar level with vessels smaller than 20 microns in diameter in multiple areas.

Shunting of blood from right to left in the heart reveals similar physiological findings as present in the proven cases of arterio-venous fistulae

of the lung. In Case 4 with a proven large atrial septal defect and pulmonary hypertension by cardiac catheterization, the saturation was only 86.5 per cent on 40 per cent oxygen breathing and 94.4 per cent on 100 per cent oxygen breathing at rest. With exercise the saturation was 54.0 per cent on air breathing and on 100 per cent oxygen breathing only 63.0 per cent. The small rise in the saturation occurring with 100 per cent oxygen breathing in conjunction with these other arterial blood saturation findings indicates that with exercise this patient is able to increase only slightly the pulmonary blood flow through the lungs. Most of the blood is simply shunting from right to left with the increased cardiac output of exercise through the septal defect which acts as a safety valve in this case. A marked increase in pulmonary vascular resistance is present and this condition is reflected by the marked decrease in the exercise oxygen uptake on air breathing (264 ml. as compared to the lower limits of normal of 500 ml. of oxygen per minute per square meter, body surface area). These measurements indicate that this patient is an unsatisfactory candidate for septal repair because of the inability to increase the pulmonary blood flow sufficiently above the resting measurements. The septal defect is acting as a safety valve in this case and to close this defect would in all probability precipitate right heart failure.

In bronchiectasis shunting of blood through nonventilated areas has been a very consistent finding especially with exercise. In Case 5 (bronchograms revealed extensive bilateral bronchiectasis) the saturation with exercise was 91.8 per cent on air breathing and even with a high oxygen breathing mixture (32 per cent oxygen) the saturation was not increased. Also intermittent positive pressure breathing on air during step-up exercise did not result in any further increase, actually slightly lower than on ambient air breathing. These figures indicate that the reduced saturation results from the perfusion of blood through nonventilated areas, as the increased inspired pO_2 was over 70 mm. Hg. on the 32.0 per cent oxygen above that on air breathing; yet no increase in saturation resulted. In this patient the resting saturation was increased from 92.7 to 96.0 per cent with intermittent positive pressure breathing on compressed air only, indicating the presence of poorly ventilated alveoli as the primary cause of the reduced saturation at rest. However, with step-up exercise the increase in the saturation did not occur with the intermittent positive pressure breathing on air, indicating that the hemodynamics of rest and exercise are different in the same individual with respect to ventilation perfusion relationships. The saturation was almost normal in this case at rest on 100 per cent oxygen breathing (98.9 per cent). The high oxygen breathing obscures inequalities of distribution at rest, which were demonstrated in this case by the intermittent positive pressure breathing on compressed air only.

In pulmonary fibrosis in the absence of a significant degree of pulmonary emphysema, the most characteristic findings on the ventilatory side consist in the reduced vital capacity and the reduced total lung capacity. Fibrosis results in a restrictive condition of the lung and there may be

no bronchospasm. Characteristic findings in pulmonary fibrosis of unknown etiology are illustrated in Cases 6 and 7, Table I. In Case 6 (Fig. 2) the resting saturation was 93.8 per cent, but it was increased to 96.4 per cent (normal) with intermittent positive pressure breathing on compressed air only, demonstrating the presence of poorly ventilated alveoli. The saturation was normal in Case 7 at rest on air breathing. In both cases, 6 and 7, the saturation was normal on 100 per cent oxygen breathing at rest (99 per cent or more). However, in both of these cases with step-up exercise on air breathing there was a marked decrease in the arterial blood oxygen saturation (84.5 per cent in one and 83.5 in the other). The exercise arterial blood oxygen saturation was repeated in both cases using a breathing mixture of 32 per cent oxygen (the inspired pO_2 was increased over 70 mm. Hg.), and in both cases a marked lowering of the arterial blood oxygen saturation was still present, 89.6 per cent in the first case and 86.8 per cent in the second case. The step-up exercise was again repeated using 100 per cent oxygen breathing, and in the first case a saturation of 93 per cent was obtained (a marked lowering for 100 per cent oxygen, and of the magnitude demonstrated in some cases with proven shunts as arterio-venous fistula) and 96 per cent in the second case (a moderate decrease for 100 per cent oxygen). The data obtained with the 32 per cent oxygen and 100 per cent oxygen breathing in these two cases indicates the difficulty producing the marked lowering of the arterial blood oxygen saturation as one of perfusion of blood through nonventilated alveoli with the increased cardiac output with exercise, and these data clearly indicate that the presence of an alveolar capillary membrane block was not a significant factor in these cases. The carbon dioxide is being blown off satisfactorily in both cases as shown by the CO_2 content

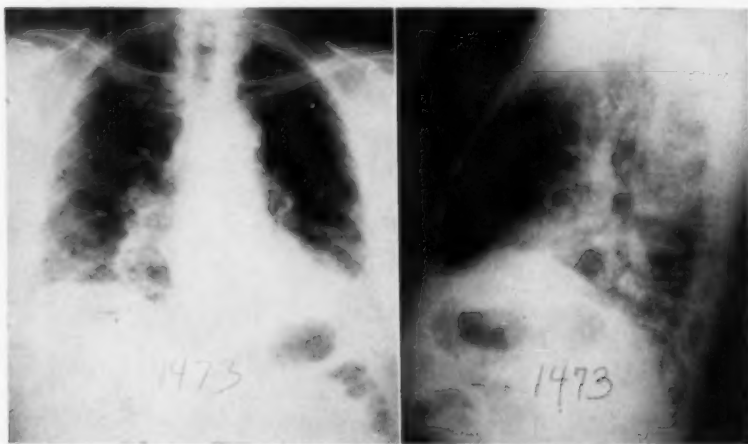


FIGURE 2: Chest roentgenogram of a 66 year old man with pulmonary fibrosis of unknown etiology. The total lung capacity was 56.0 per cent of normal predicted. Residual air was 22 per cent of total lung capacity.

and $p\text{CO}_2$ measurements. The effective tidal air was markedly decreased in the first case indicating the presence of alveoli ventilated but not perfused.

Total lung capacity is frequently markedly decreased in sarcoidosis primarily due to a reduction in the vital capacity and commonly the timed vital capacity is the same as the total indicating the absence of bronchospasm. The residual air may be reduced in similar proportion to the vital capacity. Case 8, Table I (Fig. 3) had typical clinical and x-ray findings of sarcoidosis, and this was further verified by a scalene node biopsy. In this case there was a marked reduction in total lung capacity with a marked reduction in vital capacity without a significant degree of pulmonary emphysema. The resting arterial blood oxygen saturation was quite low (87.8 per cent), and this value was markedly reduced with step-up exercise (71.6 per cent). With intermittent positive pressure breathing on compressed air only there was a significant improvement in the saturation at rest indicating the presence of some poorly ventilated alveoli which could be improved. On 100 per cent oxygen breathing at rest the saturation was normal. In this patient the exercise saturation was determined using both 32.0 per cent oxygen and 40.0 per cent oxygen breathing mixtures, and on 32.0 per cent oxygen the saturation was 78.2 per cent and with 40.0 per cent oxygen the saturation was 82.5 per cent, in both instances demonstrating a very marked decrease due to perfusion of blood through nonventilated areas with the increased cardiac output of exercise. In this case the inspired oxygen tension with exercise was increased far above that necessary to correct a diffusion difficulty of the alveolar-capillary membrane block type, if that had been the significant

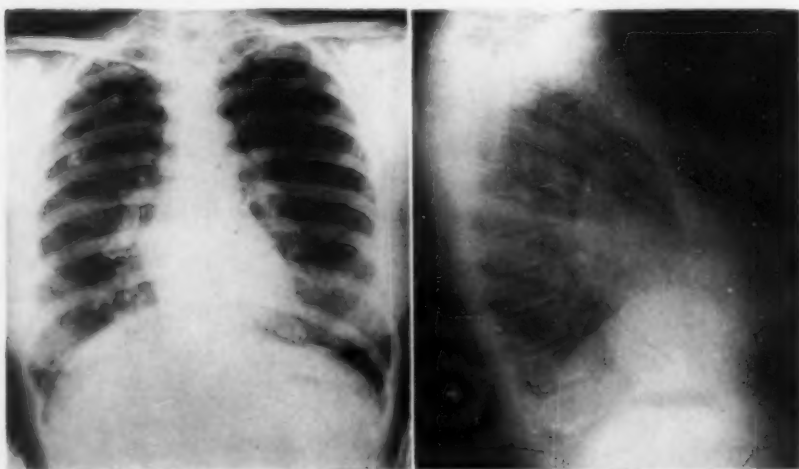


FIGURE 3: Chest roentgenogram of 32 year old woman with sarcoidosis, confirmed by scalene node biopsy. The total lung capacity was 40.7 per cent of normal predicted. Residual air was 28 per cent of total lung capacity.

factor responsible for the reduced saturation. The exercise oxygen uptake in this case was markedly decreased, although the minute ventilation was slightly increased, and this indicates the inability to increase the pulmonary blood flow corresponding to the degree of exercise given and indirectly indicates the presence of increased pulmonary vascular resistance.

Case 9 (Fig. 4) represents a most marked decrease in the total lung capacity (24.7 per cent of normal) due principally to the marked decrease in vital capacity (15.6 per cent of normal). The residual air measurement in this case was only 65.0 per cent of the normal predicted, a moderate to marked decrease; however, with very marked reduction in the total vital capacity, the residual per cent of total lung capacity is markedly increased. The diagnosis in this case has been established with practical certainty as that of lupus erythematosus based on clinical findings and L.E. cell preparation. The resting arterial blood oxygen saturation in this case was very low (76.1 per cent) and even on 32.0 per cent oxygen at rest the saturation was still significantly reduced (95.8 per cent). However, after breathing 100 per cent oxygen the saturation was increased to the normal level. With step-up exercise on air breathing there was a significant further reduction in the arterial blood oxygen saturation as compared to the resting measurement, and the saturation was markedly decreased on 100 per cent oxygen breathing with exercise (90.0 per cent). This case strikingly demonstrates the importance of comparing both rest and exercise on 100 per cent oxygen to conclusively rule out a shunt. The arterial blood oxygen saturation data in this case indicate the shunting of blood through nonventilated or very poorly ventilated areas as the reason for the unsaturation, and not by the presence of an alveolar-capillary membrane block. The exer-

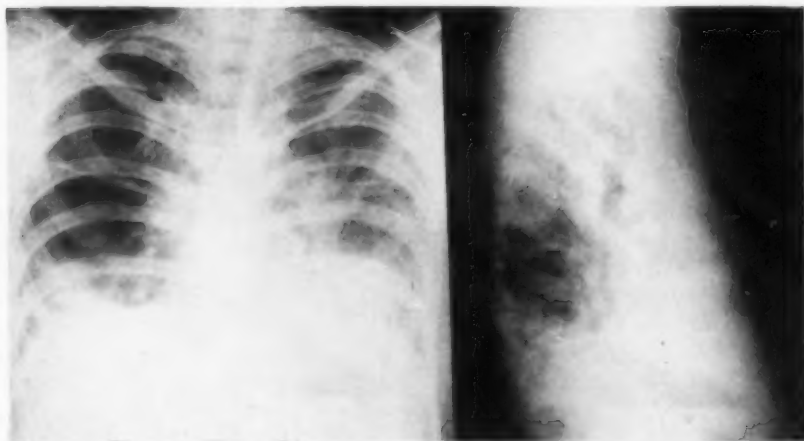


FIGURE 4: Chest roentgenogram of 22 year old man with marked decrease in total lung capacity, 24.7 per cent of normal predicted. The diagnosis has been established with reasonable certainty as lupus erythematosus. The residual air volume was 858 ml. and the vital capacity supine 773 ml.

cise oxygen uptake was markedly decreased in this case indicating the presence of increased pulmonary vascular resistance. The effective tidal air was also markedly decreased indicating the ventilation of many areas in the lung, which were not perfused. The marked reduction in the average tidal volume accounts for part of the decreased effective tidal air because of increased dead space ventilation.

Asbestosis is frequently accompanied by a significant reduction in total lung capacity, a restrictive condition with or without the presence of a significant degree of pulmonary emphysema or bronchospasm. Case 10 (Fig. 5) was an asbestosis worker of 37 years exposure with typical x-ray findings of asbestosis. There was a moderate decrease in total lung capacity accompanied by a moderate increase in the absolute value of the residual air and a moderate degree of pulmonary emphysema. The resting arterial blood oxygen saturation was decreased from 93.8 per cent at rest to 82.0 per cent with step-up exercise, a very marked decrease. The saturation was normal (99.6 per cent on 100 per cent oxygen breathing at rest). However, the saturation was markedly decreased with step-up exercise (90.5 per cent) on a high oxygen breathing mixture (32.0 per cent oxygen). With intermittent positive pressure breathing on compressed air only during step-up exercise the saturation was increased almost as much as with the 32.0 per cent oxygen breathing mixture (89.5 per cent as compared to 90.5 per cent). The exercise arterial blood oxygen saturation data in this case indicate the decrease due to perfusion of blood through nonventilated or poorly ventilated alveoli, and not due to an alveolar-capillary membrane block. Carbon dioxide was blown off adequately both at rest and with exercise.

Case 11 is that of a diatomite worker with a history of 35 years exposure to diatomaceous earth. The x-ray film revealed changes consistent with the presence of diatomite pneumoconiosis with conglomerate changes. The lung volume measurements revealed a moderate increase in the

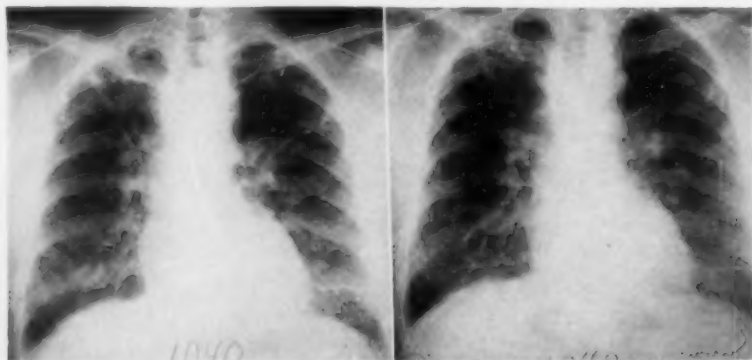


FIGURE 5: Chest roentgenogram of 58 year old man with a history of working in asbestos plant for 37 years. The vital capacity is markedly decreased without obstruction, and total lung capacity is moderately decreased.

absolute value of the residual air and a moderate degree of pulmonary emphysema. The arterial blood oxygen saturation was decreased from 92.5 per cent at rest to 84.8 per cent with step-up exercise, a marked decrease. The resting saturation was not significantly increased with intermittent positive pressure breathing in this case. The resting saturation on 100 per cent oxygen was markedly decreased, indicating extensive perfusion of blood through nonventilated areas even at rest. The exercise saturation on 32.0 per cent oxygen was markedly decreased (90.5 per cent) indicating extensive perfusion of blood through nonventilated areas. The carbon dioxide content and tension were decreased slightly at rest due to hyperventilation. The elevated alveolar-arterial pO_2 difference was due partly to the hyperventilation with the elevated mean alveolar pO_2 . Hyperventilation was quite marked with exercise and the lung ventilation efficiency was markedly decreased as shown by the reduced per cent of oxygen extracted and the decreased effective tidal air.

Pulmonary emphysema of a severe degree is characterized by an increased residual air, a decreased timed vital capacity and maximal breathing capacity, a decreased arterial blood oxygen saturation especially with exercise, an elevated CO_2 content in most cases, a decreased exercise oxygen uptake, and a decreased per cent of the effective tidal air.¹² Case 12 in Table I is typical of severe pulmonary emphysema and demonstrates the above findings. The ability to use the chest and lungs as a bellows is markedly impaired as shown by the ventilation factor at 31.6 per cent. A severe degree of hypoxia was present at rest, and this was increased slightly with exercise. Intermittent positive pressure breathing on compressed air only resulted in an increase of 6.8 per cent in the resting arterial blood oxygen saturation, a significant figure and demonstrating the presence of many poorly ventilated alveoli, a finding so characteristic of pulmonary emphysema. In this case the saturation was only 94.2 per cent on the 32.0 per cent oxygen breathing mixture indicating not only the presence of poorly ventilated alveoli, but also a significant amount of perfusion of blood through nonventilated alveoli even at rest. The saturation was also decreased on 100.0 per cent oxygen breathing at rest, 97.0 per cent (normal 99.0 per cent or more). With step-up exercise on the 32.0 per cent oxygen breathing mixture, the saturation was markedly decreased, 91.7 per cent, indicating extensive perfusion of blood through nonventilated areas and that an alveolar-capillary membrane block was not a significant factor in this case. The carbon dioxide was significantly elevated in this case both at rest and with exercise. The exercise oxygen uptake is markedly decreased, indicating a marked increase in pulmonary vascular resistance and the inability to increase the cardiac output very much above the resting level. The effective tidal air was only 45 per cent indicating the presence of many alveoli which were ventilated but not perfused.

Discussion

If the lowering of the arterial blood oxygen saturation with exercise results from a diffusion difficulty of the alveolar-capillary membrane, then

the high oxygen breathing mixture (32.0 per cent oxygen) with the resulting increased inspired pO_2 (over 70 mm. Hg.) should restore the blood saturation to a normal level of 97 per cent or more. Pulmonary emphysema and fibrosis cases in general with hypoxia on air breathing do not show a normal exercise saturation of 97.0 per cent or more on a high oxygen breathing mixture, such as 32.0 per cent, or in many cases even 40.0 per cent. The data indicate that during step-up exercise with the increased cardiac output from the right side of the heart, some blood bypasses ventilated alveoli with shunting at the alveolar level, a condition in which the use of graded level of high oxygen breathing mixtures (32.0 per cent or 40.0 per cent oxygen) does not correct. Even 100 per cent oxygen breathing does not elevate the saturation to the normal level of 99 per cent or more in all cases of severe pulmonary insufficiency. In pulmonary fibrosis and emphysema in general, the lowering of the arterial blood oxygen saturation which occurs at rest and with exercise results from alteration in the ventilation-perfusion relationship. Some alveoli are poorly aerated, yet perfused either normally or with a decreased amount of blood, other alveoli are perfused but not aerated (this latter condition represents a small shunt at the alveolar level), and some alveoli are ventilated but not perfused with blood. Furthermore, 100 per cent oxygen breathing due to the very high increase in the partial pressure of oxygen in the plasma which perfuses ventilated alveoli will tend to obscure shunting or the venous admixture at the alveolar level, whereas 32.0 per cent oxygen or 40.0 per cent oxygen breathing will not obscure the shunting at the alveolar level, yet the oxygen tension in the alveoli will be more than enough to overcome an alveolar capillary-membrane block if present on air breathing (if the block be a significant factor in producing the unsaturation).

SUMMARY

1. Our studies indicate that shunting producing arterial blood oxygen unsaturation is one of varying magnitude whether it be due to an arterio-venous fistula of the lung, intracardiac shunting from right to left or at the alveolar level in chronic pulmonary diseases such as: pulmonary fibrosis, collagen diseases, sarcoidosis, pneumoconiosis and emphysema. The decrease noted in the arterial blood oxygen saturation with exercise on air breathing was not restored to a normal level on a high oxygen breathing mixture (such as 32.0 per cent oxygen) as one would expect if the major difficulty were alveolar capillary-membrane block.

2. The use of (1) graded levels of oxygen breathing, especially 32.0 per cent oxygen and 40.0 per cent oxygen, and (2) the use of intermittent positive pressure breathing on compressed air only constitute simple tests indicating the nature of the arterial blood oxygen unsaturation.

3. The use of 100 per cent oxygen breathing at rest in an inadequate test to rule out shunting, as this not only obscures shunting at the alveolar level, but in some cases if measured with exercise a decreased saturation results in the presence of a normal resting saturation (100 per cent).

4. These studies indicate that in chronic pulmonary disease in general (except berylliosis) that the primary cause of the arterial blood oxygen unsaturation is due to the presence of poorly ventilated alveoli or to the perfusion of blood through nonventilated or poorly ventilated areas and that an alveolar-capillary membrane block is not a significant factor producing the hypoxia.

RESUMEN

1. Nuestros estudios indican que al intercomunicación que produce deficiente saturación de oxígeno en la sangre arterial es de variable magnitud ya sea que se deba a una fístula arteriovenosa en el pulmón, intercomunicación intracardiaca de derecha a izquierda, o que se establezca el nivel alveolar en enfermedades crónicas tales como: fibrosis pulmonar, enfermedades colágenas, sarcoidosis, neumoconiosis, y enfisema.

El decrecimiento observado en la saturación de la sangre arterial después del ejercicio al respirar aire, no se restauró a lo normal usando una mezcla elevada de oxígeno (tal como 32.0 por ciento de oxígeno) como uno podría esperar si la dificultad mayor fuese el bloqueo de la membrana alveolo-capilar.

2. El uso de (1) niveles graduales de oxígeno inhalado, especialmente de 32 por ciento de oxígeno y 40 por ciento de oxígeno y, (2) el uso de la respiración a presión positiva intermitente con sólo aire comprimido constituyen pruebas simples que indican la naturaleza de la insaturación sanguínea arterial.

3. El uso de oxígeno al 100 por ciento respirado en reposo es un medio inadecuado para descubrir la intercomunicación puesto que esto no sólo oscurece la intercomunicación al nivel de los alveolos sino que en algunos casos, si se mide en ejercicio, resulta una saturación disminuida en presencia de una saturación normal en reposo (100 por ciento).

4. Estos estudios demuestran que en las enfermedades pulmonares crónicas en general (con excepción de la beriliosis) la causa primaria de la insaturación arterial es la existencia de alveolas mal ventilados o la perfusión de la sangre a través de no ventilados o mal ventilados y que el bloqueo de una membrana alveolocapilar no es un factor de significación para producir hipoxia.

RESUME

1. Nos études indiquent que le shunt, ne permettant pas la saturation de l'oxygène artériel est d'importance variable selon qu'il est dû à une fistule artério-veineuse du poumon, à un shunt intra-cardiaque de droite à gauche, ou au niveau des alvéoles dans les affections chroniques du poumon, les affections étant la sclérose pulmonaire, les maladies du collagène, la sarcoïdose, les pneumoconioses, et l'emphysème. La diminution de la saturation oxygénée artérielle, après exercices respiratoires, ne peut pas être ramenée à un niveau normal par la respiration d'un mélange à haute teneur d'oxygène (tel que 32%). Tout se passe comme si l'obstacle essentiel était une obstruction de la membrane alvéolo-capillaire.

2. L'emploi de 1) taux calculés d'oxygène, particulièrement 32% et 40%; et de 2) une respiration en pression positive intermittente, sous air

comprimé, ne constituent que des tests simples qui ne permettent de connaître que la nature de la désaturation artérielle oxygénée.

3. L'emploi de la respiration oxygénée à 100% au repos est un test impropre à juguler le shunt, parce que non seulement ainsi est masqué le shunt au niveau de l'alvéole mais dans certains cas, il donne une saturation diminuée si la mesure est faite en cours d'exercice tandis que la saturation est normale au repos.

4. Ces études montrent que dans les affections pulmonaires chroniques (béryllose exceptée) la cause primaire de la non-saturation artérielle oxygénée est due à la présence d'alvéoles faiblement ventilées ou à la perfusion de sang à travers des zones non ventilées ou faiblement ventilées et que l'obstruction de la membrane alvéolo-capillaire n'est pas un facteur important d'hypoxémie.

ZUSAMMENFASSUNG

1. Unsere Untersuchungen weisen darauf hin, dass eine einen shunt bildende arterielle Blutsauerstoff-Untersättigung in ihrem Ausmass wechselt, je nach dem, ob sie die Folge einer arterio-venösen Fistel der Lunge ist, einem intracardialen Rechts-Links-shunt, oder auf der Höhe der Alveolen bei chronischen Lungenkrankheiten, wie Lungenfibrose, Bindegeweserkrankungen, Sarkoid, Pneumokoniose und Emphysem. Der Abfall in der arteriellen Blutsauerstoff-Sättigung bei Belastung unter Luftatmung wurde nicht wieder bis auf einen normalen Wert gebracht durch ein Sauerstoffhaltiges Atemgemisch (wie z.B. 32% Sauerstoff), wie man dies erwarten konnte, wenn das Haupthindernis in einem alveolarem Kapillarblock bestünde.

2. Die Benutzung von (1) abgestuften Mengen von Sauerstoffatmung, besonders 32% Sauerstoff und 40% Sauerstoff, und (2) die Benutzung intermittierender positiver Druckatmung unter komprimierter Luft stellen nur einfache Testverfahren dar, die die Natur der arteriellen Blutsauerstoff-Untersättigung anzeigen.

3. Die Benutzung einer Sauerstoffatmung von 100% bei Ruhe ist ein nicht adäquater Test zum Ausschluss eines shunt, weil des Verfahren nicht nur den shunt in Höhe der Alveolen verbirgt, sondern in manchen Fällen bei Messung unter Belastung in Gegenwart einer normalen Ruhesättigung (100%) zu einer verminderten Sättigung führt.

4. Diese Untersuchungen weisen darauf hin, dass im allgemeinen bei chronischer Lungenerkrankung (ausgenommen Berrylosis) die Hauptursache der mangelhaften arteriellen Blutsauerstoffsättigung die Folge des Vorliegens schwach beatmeter Alveolen ist oder der Blutströmung durch nicht ventilierte oder schwach ventilierte Bezirke und dass ein alveolärer Kapilar-Membran-Block kein signifikanter Faktor ist für das Zustandekommen der Hypoxie.

REFERENCES

1. Riley, R. L., Cournand, A. and Donald, K. W.: "Analysis of Factors Affecting Partial Pressures of Oxygen and Carbon Dioxide in Gas and Blood of Lungs: Methods," *J. Applied Physiol.*, 4:102, 1951.
2. Filley, G. F., MacIntosh, D. J. and Wright, G. W.: "Carbon Monoxide Uptake and Pulmonary Diffusing Capacity in Normal Subjects at Rest and During Exercise," *J. Clin. Invest.*, 33:530, 1954.

- 3 Forster, R. E., Fowler, W. S. and Bates, D. V.: "Considerations on the Uptake of Carbon Monoxide by the Lungs," *J. Clin. Invest.*, 33:1128, 1954.
- 4 Marks, A., Cugell, D. W., Cadigan, J. B. and Gaensler, E. A.: "Clinical Determination of the Diffusion Capacity of the Lungs, Comparison of Methods in Normal Subjects and Patients with 'Alveolar-Capillary Block' Syndrome," *Am. J. Med.*, 22:51, 1957.
- 5 Wilson, R. H., Evans, R. L., Johnson, R. S. and Dempsey, M. E.: "An Estimation of the Effective Alveolar Respiratory Surface and Other Pulmonary Properties in Normal Persons," *Am. Rev. Tuberc.*, 70:296, 1954.
- 6 Riley, R. L., Proemmel, D. D. and Franke, R. E.: "A Direct Method for Determination of Oxygen and Carbon Dioxide Tensions in Blood," *J. Biol. Chem.* 161:621, 1945.
- 7 Motley, H. L.: "Pulmonary Emphysema, Cardio-Respiratory Disturbance," *Dis. Chest*, 29:292, 1956.
- 8 Motley, H. L. and Tomashefski, J. F.: "Effect of High and Low Oxygen Levels and Intermittent Positive Pressure Breathing on Oxygen Transport in the Lungs in Pulmonary Fibrosis and Emphysema," *J. Applied Physiol.*, 3:189, 1950.
- 9 Motley, H. L., Smart, R. H. and Valero, A.: "Pulmonary Function Studies in Diatomaceous Earth Workers, (1) Ventilatory and Blood Gas Exchange Disturbance," *Arch. Indust. Health*, 13:265, 1956.
- 10 Evelyn, K. A. and Malloy, H. T.: "Microdetermination of Oxyhemoglobin, Methemoglobin and Sulfhemoglobin in a Single Sample of Blood," *J. Biol. Chem.*, 126:655, 1938.
- 11 Liebow, A. A., Hales, M. R., Lindskog, G. E. and Bloomer, W. E.: "Plastic Demonstrations of Pulmonary Pathology," *J. Tech. Methods*, 27:116, 1947.
- 12 Motley, H. L. and Smart, R. H.: "Pulmonary Emphysema: Physiological Factors in Diagnosis and Advances in Therapy," *J. Am. Geriatrics Soc.*, 3:316, 1955.

Comparison of 4,4'-Diaminodiphenylsulfone and Its Thymolated Derivative in Experimental Tuberculosis in Guinea Pigs

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Although 4,4'-diaminodiphenylsulfone (DDS) has definite antituberculous effects in guinea pigs infected with the human type of tubercle bacilli,¹ the toxicity of this drug has precluded its acceptance in the treatment of tuberculosis in humans. DDS and a few of its derivatives are widely used in leprosy because no other equally effective agents are available for the treatment of this disease; however, the toxicity of these drugs also limits their usefulness in this disease.² Consequently, a large number of derivatives of DDS have been prepared and studied in an effort to obtain a relatively nontoxic but active antimycobacterial drug. The evidence indicates that most of these derivatives may have no advantage over DDS itself.³⁻⁵

Of current interest is a derivative of DDS that is said to be relatively nontoxic. It is 4,4'-bis (6-thymylazo)-diphenylsulfone, which is derived from DDS by diazotization and coupling with thymol (Fig. 1). This drug will be referred to as DDS-thymol.

Therapeutic trials with DDS-thymol in tuberculous patients who failed to respond to other treatment indicated that the drug had beneficial effects and was nontoxic.^{6,7} It is reported to be nontoxic for guinea pigs,⁸ which is in contrast to the well known hematotoxic effect in guinea pigs of DDS and some of its derivatives.⁵

DDS-thymol had no therapeutic activity in experimental tuberculosis in mice.⁹ In tuberculous guinea pigs, however, the daily administration of 400 mg. of DDS-thymol increased the survival time and promoted healing of the ulcer at the site of inoculation. Also, fewer acid-fast bacilli were present in smears of various organs in comparison to the findings in untreated animals.¹⁰

The following report describes a study in which it was found that administration of DDS-thymol to tuberculous guinea pigs resulted in regression and healing of lesions as determined by gross and histopathologic examination. This compound appeared to be less effective than DDS but it was less toxic.

Methods

Each of 36 mature male guinea pigs, weighing approximately 600 gm. apiece, received an intraperitoneal injection of 0.1 mg. (moist weight) of virulent human-type tubercle bacilli (H37Rv). On the 16th day after infection, six animals were killed to obtain evidence that a progressive disease had been established; these six animals were the pretreatment

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controls. On the same day, the remaining 30 animals were divided into three groups of 10 animals each as follows: (1) controls; (2) those treated with DDS,* 0.5 per cent in the diet; (3) those treated with DDS-thymol,* 1.0 per cent in the diet. All animals were fed Purina rabbit chow** to which was added 0.1 per cent of ascorbic acid.

The drugs (in powdered form) were mixed daily with the diet. The amount of DDS-thymol was selected somewhat arbitrarily. A preliminary trial showed that normal guinea pigs continued to gain weight when fed a diet containing 1.0 per cent of DDS-thymol. The amount of DDS was selected on the basis of unpublished observations showing that a diet containing 0.5 per cent of DDS, although hematotoxic, had a great therapeutic effect on tuberculosis in guinea pigs.

Six of the control animals had died by the 131st day of infection, and three of the four remaining controls were losing weight. Therefore, the experiment was discontinued on the 132nd day of infection (116 days of treatment). All surviving animals were killed. The lesions seen at necropsy were recorded schematically as shown in Figure 2. Suitable portions of tissue were preserved for histopathologic examination.

Results

Mortality.—As already indicated, six of the control animals had died by the 131st day of infection (Fig. 2). Of those given DDS-thymol, two died after only 3 and 20 days of treatment, respectively, and were considered as failures. Two other animals in this group died after 53 and 81 days of treatment, respectively. No deaths occurred in the group treated with DDS.

Gross and Histopathologic Observations.—The animals killed on the 16th day of infection (pretreatment controls) had visible lesions in the liver and spleen (Fig. 2); small tuberculous foci were seen microscopically in the lungs. It is presumed that the disease in the remaining animals, when the treatment period started, was comparable to that in the pretreatment controls. The lesions in the control animals were typical of the widespread destructive tuberculous process usually seen in experimentally infected guinea pigs.

In the group treated with DDS-thymol, the two animals considered as failures had lesions similar to those of the controls, as did also the two animals which died after 53 and 81 days of treatment. Of the six animals which received treatment for the entire 116-day period, one had a few visible lesions in the liver. This animal, as well as two others, had small but active microscopic caseous foci in the lungs. Aside from this, sections of lungs, liver and spleen of the animals given DDS-thymol contained no other microscopic evidence of actively progressing tuberculous foci. However, caseous lesions were present in the tracheobronchial, hepatic and iliac lymph nodes of each animal.

*The DDS and DDS-thymol were obtained from Dr. E. F. Roberts, Wyeth Laboratories, Philadelphia, Pennsylvania.

**Purina rabbit chow is manufactured by the Ralston Purina Company, St. Louis, Missouri.

Of the animals treated with DDS, two had multiple miliary lesions in the lungs visible at necropsy and two others had small caseous pulmonary lesions demonstrable microscopically. Peculiarly, active lesions were not seen in sections of liver or spleen of the four animals with pulmonary lesions. Sections of lungs, liver and spleen of the other animals in this group were free of active tuberculous disease. However, caseous foci were present in the tracheobronchial, hepatic and iliac lymph nodes of all the animals treated with DDS.

The index of infection, based on the extent and character of the lesions as determined histopathologically,¹¹ was as follows: pretreatment controls, 55; controls, 90; those receiving DDS-thymol, 1.0 per cent in the diet, 30.0; those receiving DDS, 0.5 per cent in the diet, 15.0. The index for the animals treated with DDS-thymol includes the two which died after 53 and 81 days of treatment. If these are excluded, an index of 20 was determined for the six animals treated during the entire 116-day period.

Toxicity.—Although this study was made primarily to determine the therapeutic effect of DDS-thymol, certain limited observations suggest that this drug was well tolerated. The animals gained weight during the period of treatment. Sections of kidneys, lungs, liver and spleen showed no morbid changes that could be attributed to the drug.

The hematotoxic effects of DDS were manifested by the enlargement and the deep-purple color of the spleens of all animals in this group. Microscopically, the splenic sinusoids were greatly distended. Numerous pigment-laden macrophages lined the sinusoids and also were situated within the splenic cords. This pronounced change in the structure of the spleen was not seen in the animals given DDS-thymol.

Comment

These results show that the administration of DDS-thymol to tuberculous guinea pigs resulted in regression of the disease but give no indication

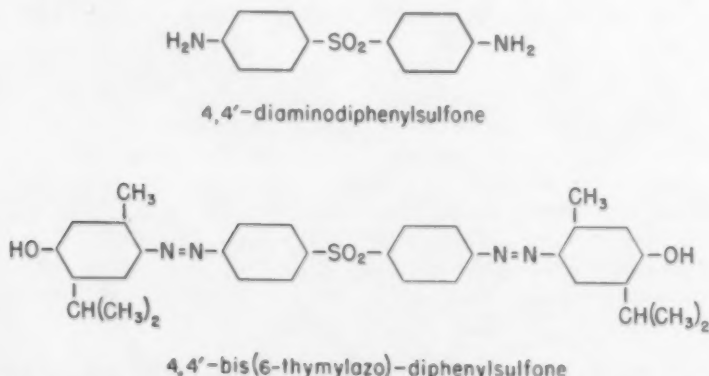


FIGURE 1: Structural formula of 4,4'-bis (6-thymylazo)-diphenylsulfone (molecular weight 570.7) compared to that of 4-4'-diaminodiphenylsulfone (molecular weight 248.3).

of the mode of action of the drug. There is a question as to whether DDS-thymol acts directly or owes its effect to the liberation of DDS. According to Rist and associates,⁹ 90 per cent of the DDS-thymol given orally to mice is eliminated in the feces, which accounts for its inactivity against tuberculosis in this species. These workers considered that the reported low toxicity of DDS-thymol is due to the fact that it is stable and releases only small amounts of DDS in vivo. Furthermore, Rist's group ascribed the reported beneficial effects of DDS-thymol in tuberculosis and leprosy to liberation of small amounts of DDS over a prolonged period of therapy. In guinea pigs, on the other hand, Cotereau and associates^{12, 13} reported that DDS-thymol is absorbed and is present in the blood in concentrations as much as 20 times those of the DDS which is liberated. These workers thought that DDS-thymol acts directly and does not owe its effect to the release of DDS.

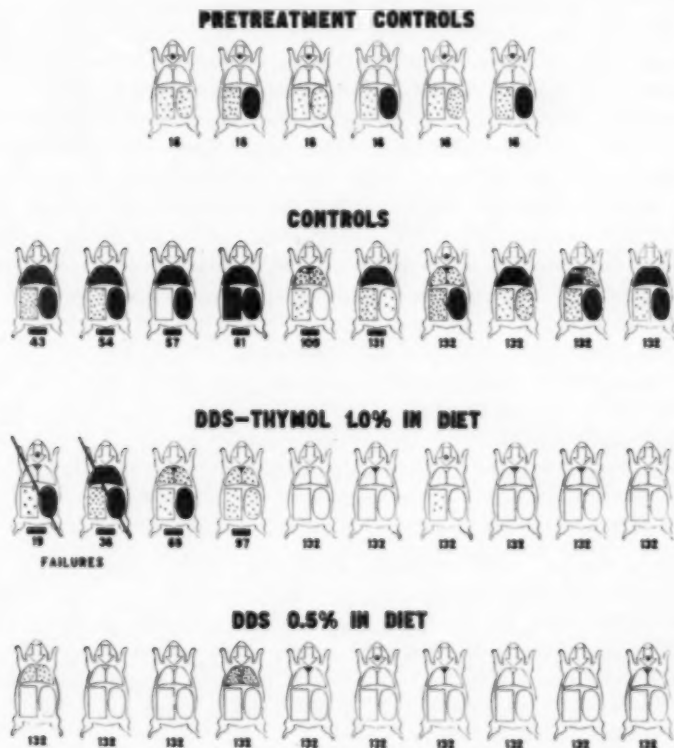


FIGURE 2: Schematic representation of the lesions seen at necropsy. The numbers below each animal indicate the duration of infection in days; the black bar indicates that the animal died. The oval and rectangle represent spleen and liver, respectively; the dots indicate miliary or nodular lesions, whereas complete blackening means diffuse tuberculous involvement. A dot in the arrow indicates involvement of retrosternal lymph nodes. Two animals given DDS-thymol are considered failures because they died prematurely.

In the present study, three animals died after 20, 53 and 81 days of treatment, respectively, with no evidence of any therapeutic effect from DDS-thymol. This may have been the result of poor absorption, which, however, was sufficient for a cumulative effect in animals treated for 116 days. A second possibility is that DDS-thymol does not act directly but owes its effect to liberation of DDS in amounts that are not toxic but are sufficiently great to account for the therapeutic benefit.

SUMMARY AND CONCLUSIONS

Each of 36 guinea pigs was infected intraperitoneally with virulent tubercle bacilli. After 16 days, six were killed and found to have tuberculous lesions. On the same day, the remaining animals were divided into three groups of 10 animals each, namely controls, those treated with 4,4'-diaminodiphenylsulfone (DDS), and those treated with DDS-thymol. Treatment continued for 116 days, at which time all survivors were killed. Six controls had died by this time. All controls, including four survivors, had extensive tuberculosis.

Of those animals treated with DDS-thymol, two died prematurely; two others died after 53 and 81 days of treatment, respectively, and had extensive lesions. Of the surviving six animals, one had a few residual foci in the liver and lungs and two others had microscopically evident lesions in the lungs only. All had caseous lesions in lymph nodes. None of these animals showed any toxic effect from the drug.

None of the animals given DDS died; four had evidence of pulmonary tuberculous lesions. All had caseous foci in the lymph nodes and enlarged cyanotic spleens with dilated sinusoids and many pigment-laden macrophages.

The administration of DDS-thymol to tuberculous guinea pigs resulted in regression of the disease, but the beneficial effect was less than that of DDS. The hematotoxic effects of DDS, as determined by splenic changes, were not seen in animals given DDS-thymol. It was not determined whether DDS-thymol has a direct action or if it is active because of DDS liberated *in vivo*.

RESUMEN Y CONCLUSIONES

Se infectaron con bacilo tuberculoso virulento 36 cuyes, usando la vía intraperitoneal. Después de 16 días, seis se sacrificaron y se encontró que tenían lesiones tuberculosas. El mismo día los animales restantes se dividieron en tres grupos de 10 cada uno o como controles, el segundo grupo se trató con 4,4'-diaminodifenilsulfona (DDS) y el otro grupo con DDS-timol. El tratamiento se prolongó por 116 días a cuyo término se sacrificaron todos los sobrevivientes.

Durante este tiempo murieron seis controles. Todos los controles incluyendo los sobrevivientes tenían tuberculosis extensa.

De los animales tratados con DDS-timol dos murieron prematuramente; otros dos murieron después de 53 y 81 días de tratamiento respectivamente y tenían lesiones extensas. De los sobrevivientes seis animales, uno tenía

un foco residual en el hígado y otros dos tenían lesiones microscópicas evidentes sólo en los pulmones. Todos tenían lesiones caseosas en los ganglios. Ninguno de estos animales mostró efecto tóxico por la droga.

Ninguno de los animales a los que se dió DDS murió; cuatro tenían evidencias de tuberculosis pulmonar. Todos tenían focos caseosos en los ganglios linfáticos y bazos crecidos y cianóticos con sinusoides ensanchados y muchos macrófagos cargados de pigmento.

La administración de DDS-timol a los cuyes tuberculosos produjo regresión de la enfermedad pero el efecto benéfico fué menor que en los tratados por DDS según se determinó por los cambios esplénicos que no se vieron en los que recibieron DDS-timol.

No se determinó si el DDS-timol tiene una acción directa o si es activo por la liberación de DDS en vivo.

RESUME

36 cobayes furent inoculés chacun par voie intrapéritonéale avec des bacilles tuberculeux virulents. Après 16 jours, six furent tués et on constata qu'ils étaient porteurs de lésions tuberculeuses. Le même jour, les animaux restant furent divisés en trois lots de dix animaux, les témoins, ceux traités par le 4,4'-diaminodiphénylsulfone (DDS) et ceux traités par le DDS-thymol. Le traitement fut poursuivi pendant 116 jours, au bout desquels tous les survivants furent sacrifiés. Six témoins étaient morts pendant ce temps. Tous les témoins, y compris les quatre survivants, étaient atteints de tuberculose extensive.

Parmi ceux des animaux traités par le DDS-thymol, deux moururent prématurément; deux autres moururent après 53 et 81 jours de traitement avec des lésions extensives. Sur les six animaux survivants, l'un présentait quelques foyers résiduels au foie et aux poumons, et deux autres des lésions visibles microscopiquement uniquement dans les poumons. Tous présentaient des lésions caséuses dans les ganglions. Aucun de ces animaux ne montra le moindre syndrome toxique imputable à la médication.

Aucun des animaux que avaient reçu du DDS ne mourut; quatre avaient des lésions tuberculeuses pulmonaires évidentes. Tous avaient des foyers caséux dans les ganglions, et des rates cyanosées et volumineuses, avec des sinus dilatés et chargés de macrophages pigmentés.

L'administration de DDS-thymol aux cobayes tuberculeux a permis la régression de l'affection, mais l'effet favorable fut moindre que celui du DDS. Les effets hémato-toxiques du DDS, comme ils ont été révélés par les altérations de la rate, n'ont pas été constatés chez les animaux traités par le DDS-thymol. Il n'a pas été possible de savoir si le DDS-thymol a une action directe ou s'il est actif grâce au DDS libéré *in vivo*.

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNGEN

Ein jedes von 36 Meerschweinchen wurde intraperitoneal infiziert mit virulenten Tuberkelbazillen. Nach 16 Tagen wurden 6 getötet und bei ihnen tuberkulöse Herde gefunden. Am gleichen Tag wurden die übrigen Tiere in 3 Gruppen von je 10 Tieren eingeteilt, nämlich die Kontrollen,

solche, die mit 4,4'-Diaminodiphenylsulfon (DDS) behandelt wurden, und schliesslich die mit DDS-Thymol behandelt wurden. Die Behandlung wurde 116 Tage lang fortgesetzt und zu diesem Zeitpunkt alle überlebenden Tiere getötet. 6 Kontrolltiere waren während dieser Zeit umgekommen. Alle Kontrolltiere einschl. der 4 Überlebenden hatten eine ausgedehnte Tuberkulose.

Von den mit DDS-Thymol behandelten Tieren starben 2 vorzeitig; 2 andere starben nach 53 und 81 Tagen der Behandlung und hatten ausgedehnte Veränderungen. Von den überlebenden 6 Tieren hatten einige wenige Restherde in der Leber und Lunge, und 2 andere hatten nur mikroskopisch sichtbare Lungenherde. Alle wiesen Käseherde in den Lymphknoten auf. Keines dieser Tiere legte irgendwelche toxischen Wirkungen des Medikamentes an den Tag.

Keines der Tiere, die DDS bekommen hatten, starb. 4 hatten Anzeichen von pulmonalen tuberkulösen Herden. Alle hatten Käseherde in den Lymphknoten und eine vergrösserte cyanotische Milz mit erweiterten Sinus und zahlreichen pigmenthaltigen Makrophagen.

Die Verabreichung von DDS-Thymol an tuberkulöse Merschweinchen hatte eine Rückbildung der Erkrankung zur Folge, jedoch war die Heilwirkung geringer als diejenige von DDS. Die haematotoxischen Wirkungen von DDS, wie sie sich aus den Milzveränderungen ergaben, war nicht bei den mit DDS-Thymol behandelten Tieren zu sehen. Es wurde nicht ermittelt, ob DDS-Thymol eine direkte Wirkung hat, oder ob es aktiv ist durch in vivo frei gewordenen DDS.

REFERENCES

- 1 Feldman, W. H., Hinshaw, H. C. and Moses, H. E.: "The Effects on Experimental Tuberculosis of 4,4'-Diaminodiphenylsulfone," *Am. J. M. Sc.*, 207:290, 1944.
- 2 Doull, J. A.: "Progress in the Therapy of Leprosy," *Congresso Internazionale per la Difesa e la Riabilitazione Sociale del "Lebrossa"*, Rome, April 16-18, 1956, pp. 95-106.
- 3 Dharmendra: "Chemotherapy of Leprosy," *Indian M. Gaz.*, 88:35, 1953.
- 4 Francis, J. and Spinks, A.: "Antibacterial Action and Metabolism of Five Sulfones," *Brit. J. Pharmacol.*, 5:565, 1950.
- 5 Feldman, W. H.: "An Evaluation of the Efficacy in Tuberculosis of Sulfonamides, Sulfones and Certain Other Substances," *J. Roy. Inst. Pub. Health and Hyg.*, 9: 297, 1946.
- 6 Weiller, Pierre and Rymer, Maurice: "A propos d'une nouvelle sulfone et de son intérêt dans le traitement de la tuberculose pulmonaire," *Poumon, Par.*, 8:747, 1952.
- 7 Chortis, P.: "La contribution de la sulfone thymolée au traitement de la tuberculose," *Poumon and Coeur*, 11:487, 1955.
- 8 Salomon, L.: Quoted by Weiller, Pierre and Rymer, Maurice.⁶
- 9 Rist, Noel, Boyer, Fernand, Saviard, Micheline and Hamon, Viviane: "Sur le mode d'action d'une sulfone thymolée argentique," *Rev. tuberc., Paris*, 18:179, 1954.
- 10 Urquia, D. A.: "Propriétés bacteriostatiques d'une sulfone thymolée," *Compt. rend. Soc. biol.*, 149:1948, 1955.
- 11 Feldman, W. H.: "A Scheme for Numerical Recording of Tuberculous Changes in Experimentally Infected Guinea Pigs," *Am. Rev. Tuberc.*, 48:248, 1943.
- 12 Cotereau, H. Y., Marquiset, J. P., Chaslot, M. and Delamarre, E.: "Recherches biochimiques sur une sulfone thymolée et son dérivé argentique (J51)," *Compt. rend. Soc. biol.*, 149:1142, 1955.
- 13 Cotereau, H. Y., Marquiset, J. P., Chaslot, M. and Delamarre, E.: "Nouvelles recherches sur la sulfone bisazoïque thymolée," *Compt. rend. Soc. biol.*, 149:1950, 1955.

A New Effective Method of Nebulizing Bronchodilator Aerosols: Clinical and Physiological Effects

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The use of bronchodilators by nebulization in the treatment of bronchopulmonary disease is recognized to be the most effective and simplest method for control of bronchospasm.

The problem of propulsion of aerosols has been treated in various manner by investigators.¹⁻³ High pressures needed to achieve the breaking up of solutions into fine particles has been attained in the past by the use of such various devices and propellants as hand bulbs, foot pumps, electric pumps, oxygen and the liquid phase of fluorinated hydrocarbons. The difficulties in coordination between the patient's inhalation and the compression of a hand bulb results at times in failure to achieve a bronchodilator effect of the aerosols administered. The use of the liquid phase of fluorinated hydrocarbon as utilized in a metered valve nebulizer⁴ has the disadvantages of difficulty in controlling particle sizes and the irritating effects of the marked cooling of the aerosol produced at the site where the medication is broken up into a stream of fine particles, from where it is carried in its cold state in the pharynx, larynx, and trachea.

The main objective of this study was to establish the usefulness of the gaseous phase of dichlorodifluoromethane** as a means of propelling bronchodilator aerosols. The low degree of toxicity of this gas in mice, rats, guinea pigs, dogs and monkeys^{5, 6} in concentrations up to 20 per cent in the inspired air with exposure time of seven to eight hours daily for 12 weeks, as well as its nearly ideal physical characteristics, suggests its potential value for this purpose. The good control of aerosol particle size which can be achieved as well as the markedly reduced cooling effect at the site of aerosolization, when the gas phase of dichlorodifluoromethane is used, further stimulated interest in the employment of this form of propellant. A clinical appraisal of these theoretical advantages appeared indicated. Determination of the effects of dichlorodifluoromethane on the bronchopulmonary tree, in patients with bronchospasm

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**The gas phase of dichlorodifluoromethane is 99.98 per cent pure, and contains no hydrocarbons; cartridges containing this gas were supplied as Halon® (formerly Halothane) by Thomas J. Mahon, Inc., Englewood Cliffs, New Jersey.

were thought to be useful. A further object of this study was to utilize a nebulizing unit which would combine the advantages gathered from theoretical considerations of the most effective particle size, with practicality of use for the patient and to determine its effectiveness as compared to other types of nebulizers. A clinical evaluation of a gas phase nebulizer was performed using 0.5 per cent isoproterenol hydrochloride* or 2.25 per cent racemic epinephrine** as bronchodilators. A series of twenty patients was studied with respect to the inhalation of a mixture of 0.4 per cent isoproterenol sulfate and 2.0 per cent phenylephrine.† These studies were also accompanied by determination of vital capacities, changes in blood pressure and heart rates.

Introduction and Methods

Since the introduction of aerosols for the treatment of bronchospasm several definite principles have been established. Two of the principles concerned the deposition of particles in the tracheobronchial tree:^{1,7}

1. The smaller the particle size of aerosol above 0.8 micron, the closer to the alveoli and to the alveolar ducts its deposition in the lungs; the larger its size the higher its rate of deposition in the upper respiratory tree.

2. The smaller the particle size, the lower the per cent of retention in the lung, a condition which prevails when the diameter of the particle is between 0.2 and 0.6 microns.^{8,9}

It has been recommended¹⁰ that 50 per cent or more of the particles delivered have a range of diameter between 1 and 5 microns. The experimental attempts to achieve this particle size, utilizing the liquid phase of fluorinated hydrocarbon as a propellant have been unsuccessful. A high percentage of larger particles causes the aerosol to be "wet," thereby producing deposition of a large proportion of the drug-fluorinated hydrocarbon mixture in the upper respiratory tract, causing throat irritation. The observation that the gas phase of dichlorodifluoromethane, exerting an absolute pressure of 70 lbs. per square inch at 21°C., offered an excellent and well tolerated source of propulsion led to the development of a simple experimental nebulizer (Fig. 1A). Two pocket sized cartridges containing 51 and 100 gms. of dichlorodifluoromethane, respectively, in its liquid-gas equilibrium were utilized as sources of propulsion. Since the pressure exerted by dichlorodifluoromethane gas does not vary with the amount of liquid or gas present in a cartridge, 70 lbs. per square inch is available for propulsion of the aerosol, as long as any amount of

*0.5 per cent isoproterenol hydrochloride (Nepu-Prel) and a mixture of 0.4 per cent isoproterenol sulfate and 2.0 per cent phenylephrine in 10 per cent propylene glycol (Nebu-prel with phenylephrine), were supplied by Thomas J. Mahon, Inc., Englewood Cliffs, N. J.

**2.25 per cent racemic epinephrine (Vaponefrin) was supplied by Vaponefrin Co., Upper Darby, Pennsylvania.

†cf. Foot Note ** on page 2.

dichlorodifluoromethane is present within the cartridge. Through a lateral displacement valve the pressure available from the cartridge is transmitted to a nebulizer, which by venturi action picks up the bronchodilator from a small well and throws it against a baffle, thereby breaking it up into a desirable size of particle. Activation of the valve was simply effected by slight sideways pressure of the nebulizer. An air vent in the back of the venturi-baffle device of the nebulizer served, in the manner of a carburetor, to increase the impact of the bronchodilator stream against the baffle, thereby still further decreasing particle size, and also increasing the total aerosol flow into the patient's mouth by admixture of air to the propellant gas. A further modification of this type nebulizer was developed in which a replaceable cartridge and nebulizing unit are contained within one small plastic unit, in which the release of dichlorodifluoromethane is effected by slight displacement of the cartridge, rather than the nebulizer, using slight pressure of the thumb.* In addition, this unit has the advantage of replaceable capillaries, easy access to the interior of both the cartridge chamber and the aerosol well for cleaning purposes (Fig. 1B).

The patient is instructed to activate this unit by slight pressure of the thumb against the cartridge through the hole in the cartridge housing,

*Nebu-Halent® "Touch-Action" Nebulizer, as supplied by Thomas J. Mahon, Inc., Englewood Cliffs, N.J.



FIGURE 1A

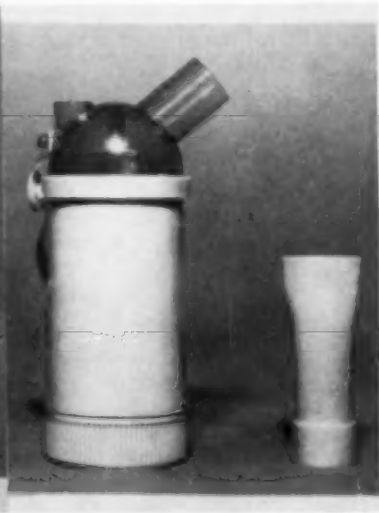


FIGURE 1B

Figure 1A: Halon® gas phase propelled nebulizer. Experimental model.—Figure 1B: Halon® gas phase propelled nebulizer. Clinical apparatus.

simultaneously with the initiation of his own inspiration, placing the spout of the nebulizer about one inch in front of the mouth.

Dichlorodifluoromethane concentrations inhaled during the process of aerosolization were measured in the following manner: A plastic catheter was introduced through the nose into the subject's pharynx, about 1 cm. above the epiglottis. The gas sample was collected in a mercury sampling bottle slowly throughout each of five consecutive inspirations, while the subject was inhaling the gas mixture from the nebulizer. The sampling bottle then was emptied through the catheter to wash out the dead space with inspired air. The procedure was then repeated. The gas sample thus collected was analyzed for oxygen and carbon dioxide, using the Scholander Method of Analysis.* The concentration of dichlorodifluoromethane in the inspired air calculated from the reduction in the oxygen concentration in the sample from that of ambient air, was 3.7 per cent. Up to 8.1 per cent of dichlorodifluoromethane were obtained during the early part of the inspiration when the gas samples were collected under vacuum.

The studies determining the particle size produced by the unit were conducted using a cascade impactor** 0.5 per cent isoproterenol hydrochloride solution to which radioactive and phosphorus-32 was added in the proportions of 250 microcuries P 32 to 10 cc. of bronchodilator.

Vital capacity studies were performed graphically in some patients, by using a 9 liter spirometer and by means of inflation of a McKesson Scott Ventilometer in others. The vital capacity, heart rate and blood pressure measurements were carried out immediately before, and 10 to 15 minutes after the inhalation of the aerosol. The patients were selected strictly at random† in all experiments to determine which medication they should receive.

Isoproterenol hydrochloride and 2.25 per cent racemic epinephrine were selected as bronchodilators in this study because of the known high degree of effectiveness of these medications in resolving bronchospasm.^{1, 3, 11-13} A quantitative comparison of the effectiveness of these bronchodilators when inhaled by the dichlorodifluoromethane gas phase propelled nebulizer was attempted. Additional information concerning differences in the physiological effects of these two drugs in pulmonary emphysema and bronchial asthma, with particular reference to vital capacity, blood pressure, heart rates, and the side effects, was thought to be desirable. A mixture of 0.4 per cent isoproterenol sulfate and 2 per cent phenylephrine hydrochloride, administered in the same manner was similarly studied to determine the

*The gas analyses were performed in the Laboratories of Doctor Duncan Holaday, Department of Anesthesiology, Columbia University, College of Physicians and Surgeons, New York, N.Y.

**This study was performed at the Battelle Memorial Institute, Columbus, Ohio, by R. I. Mitchell.

†The term "strictly at random" has been recommended by D. Mainland, *Chance and Random Sampling, Methods in Medical Research*, Vol. 6, 1954, J. Murray Steele, Ed., The Year Book Publishers. It signifies the selection of samples by means of an unbiased method of chance, e.g., the throw of a coin.

possible advantages of the addition of a vasoconstrictor to a bronchodilator aerosol.¹

Results

Ten patients with bronchial asthma and pulmonary emphysema were given five inhalations of dichlorodifluoromethane from the nebulizing unit described, without the addition of a bronchodilator. The chest was examined and vital capacities performed before and 10 minutes after the inhalation of the propellant. The patients were also asked if they noted any side effects. The results summarized in Table I, revealed that dichlorodifluoromethane produced no significant changes in vital capacity. Only one complained about the odor of gas, stating that it resembled that of ether and that he never liked ether. The degree of wheezing remained the same in all, except in two where it seemed that a slight diminution had taken place, and that there was slightly diminished dyspnea.

One hundred patients with bronchial asthma or pulmonary emphysema were supplied with dichlorodifluoromethane propelled units and either 2.25 per cent racemic epinephrine or 0.5 per cent isoproterenol hydrochloride for use at home over periods of one to six months. The following information was requested from the users:

1. Number of daily single inhalations.
2. Number of total inhalations which could be obtained from one single Halon® cartridge.
3. Comparison of effectiveness and ease of administration of the dichlorodifluoromethane propelled with other types used before.

The average number of daily single inhalations using dichlorodifluoromethane cartridges was 24. The average number of days of use of one cartridge was nine. No respiratory tract or gastrointestinal tract irritation was observed. The ethereal odor of dichlorodifluoromethane was found objectionable by three patients. Headache was reported in two patients, dizziness by the same two patients and one additional patient. The latter also described faintness and tremors following the use of bronchodilator aerosols in general. For this reason he was tested in the clinic using five inhalations of dichlorodifluoromethane without the bronchodilators; he had none of these side reactions under these circumstances. Similarly, six others who reported tremulousness and palpitation following five inhalations of bronchodilator aerosols reported none of these symptoms if dichlorodifluoromethane was inhaled without a bronchodilator or if the number of inhalations with bronchodilators was reduced to two or three per treatment. They all had, also, a good bronchodilator response from this diminished dose.

Thirty-two patients, described better bronchodilating effects from the gas phase type nebulizing unit than with any other type unit used up to that time. Better coordination between their own inspiration and activation of the dichlorodifluoromethane propelled nebulizer probably accounted

for this observation. Two refused to continue using the equipment, both because of headache, faintness and dizziness following its use.

Determination of the particle size and distribution of the number of particles in various ranges are summarized to Table II.* The mass median diameter of the particles produced by the dichlorodifluoromethane gas phase propelled nebulizer with the air vent open was 1.9 microns. The weight fractions of particles having a diameter of 1 to 5 microns was 70 per cent, that fraction containing large particles of a diameter of 5 microns being only 14 per cent.

Determinations of the amounts of 0.05 per cent isoproterenol hydrochloride solution aerosolized revealed that 0.012 mg. were inhaled per breath.

Vital capacity determinations performed before and 10 minutes after five single inhalations of isoproterenol hydrochloride and 2.25 per cent racemic epinephrine in patients with pulmonary emphysema and bronchial asthma, are summarized in Table III and IV. The mean per cent increase over the control value were 36 per cent in bronchial asthma and 34 per cent in pulmonary emphysema for 2.25 per cent racemic epinephrine, and 30 per cent in bronchial asthma and 29 per cent in pulmonary emphysema for 0.05 per cent isoproterenol hydrochloride. The difference as calculated by determining t-values were statistically insignificant for the two bronchodilators in bronchial asthma or pulmonary emphysema.

The blood pressures of patients using isoproterenol hydrochloride and racemic epinephrine by this method of aerosol administration were studied in normotensive and hypertensive patients with bronchial asthma before and 15 minutes after administration and over a period of three months. The results are summarized in Table V. The mean systolic and diastolic blood pressure differences, before and 15 minutes after administration of five inhalations of these two bronchodilator drugs, normotensive and hypertensive patients were not significant. In twenty patients in whom three inhalations of the 0.4 per cent isoproterenol sulfate and 2.0 per cent phenylephrine was given a single treatment in the office or the Out-Patient Department the clinical results were good. This patient group included those with pulmonary emphysema and bronchial asthma, many of whom were getting worse on routine therapy. An increase in vital capacity occurred in all instances (Table V). In an additional group of ten patients, in which five inhalations of this compound was administered, a somewhat more pronounced improvement took place both to subjective relief and vital capacity change. In patients to whom isoproterenol combined with phenylephrine was administered sinus tachycardia was not observed. No significant change in blood pressure was found (Table VI).

Sinus tachycardia occurred in five patients (10 per cent) following five inhalations of isoproterenol hydrochloride, and in three patients (6 per

*This study was performed at the Battelle Memorial Institute, Columbus, Ohio, by R. I. Mitchell.

cent) using 2.25 per cent racemic epinephrine. The incidence of tachycardia was not related to the presence of either hypertension or heart disease. In no instance did the heart rate exceed 130 beats per minute. Palpitation occurred in one of these patients using isoproterenol hydrochloride.

Discussion

The frequent use of dichlorodifluoromethane as a refrigerant and the reported low degree of toxicity in animals by inhalation in concentrations up to 20 per cent warranted its use as a propellant for bronchodilator aerosols. It would appear from this study that the compound in concentrations of about 4 per cent in the inspired air behaves as an inert gas as far as its inhalations by patients with bronchial asthma and pulmonary emphysema are concerned.

A device was designed utilizing the gaseous phase of dichlorodifluoromethane as a propellant and incorporating the advantages of nebulizers known to exist, including dispersion into desirable particle size, efficiency of pick-up of aerosol by the capillary of the venturi, simplicity in activating the nebulizer and exchangeability of capillaries.

The observations of the effectiveness of aerosols administered by this method as measured clinically and by means of vital capacity measurement may be ascribed to greater ease of coordination between activation of the device and the patient's initiation of inspiration. High volume flow rates occurring during the first part of inspiration in patients with bronchospasm carry the aerosol particles of optimal particle size to the small bronchi.

The absence of short or long term effects on the blood pressure of normotensive and hypertensive patients of inhaled isoproterenol hydrochloride with and without phenylephrine and 2.25 per cent racemic epinephrine is of clinical importance. One may conclude from the findings in this series that the use of these sympathomimetic amines in hypertensives has little or no deleterious effect on the level of either the systolic or the diastolic blood pressure, if the range of the particle size is sufficiently controlled to permit deposition of a majority of particles on the bronchial mucosa. It is noteworthy that the bronchodilator compound containing both isoproterenol sulfate and phenylephrine did not appear to produce the tachycardia observed at times after the employment of the preparations noted above. Additional studies of this bronchodilator aerosol are in progress.

SUMMARY

The gas phase of dichlorodifluoromethane is a well tolerated and expedient propellant for use in the nebulization of bronchodilator aerosols. Inhalation in concentrations of approximately 4 per cent in patients with bronchospasm produces no change in vital capacity. Side reactions from

the inhalation of these low concentrations of dichlorodifluoromethane are minimal and occur infrequently.

Studies of the effect of 0.5 per cent isoproterenol hydrochloride and 2.25 per cent racemic epinephrine when inhaled in the form of an aerosol by means of a gas phase of dichlorodifluoromethane propelled nebulizer revealed clinical relief of dyspnea and corresponding increases in vital capacity. The number of side reactions to these bronchodilators was low and confined to tremulousness and tachycardia. Reduction in the amount of drug inhaled reduced the incidence of side reactions. The use of the bronchodilator solution in which 0.4 per cent isoproterenol sulfate was combined with 2.0 per cent phenylephrine was not followed in this series with either tremulousness or tachycardia. Neither drug caused change in the blood pressure of normotensive or hypertensive patients when nebulized with this type device.

RESUMEN

El diclorodifluorometano en fase gaseosa, es un propulsor bien tolerado y rápido para uso en nebulización de aerosoles broncodilatadores. Su inhalación en concentraciones de aproximadamente un 4 por ciento en pacientes con broncoespasmo, no produce ningún cambio en la capacidad vital.

Efectos secundarios a la inhalación de estas bajas concentraciones de diclorodifluorometano son mínimas y ocurren raramente.

Estudios del efecto de 0.5 por ciento de hidrocloreuro de isoproterenol y 2.25 por ciento de epinefrina racémica inhalados en forma de aerosol por medio de una fase gaseosa de diclorodifluorometano como propulsor nebulizador, reveló alivio clínico de disnea y subsecuente aumento de la capacidad vital. El número de efectos secundarios a estos broncodilatadores fué bajo y confinado solamente a temblor y taquicardia. Reducción de la cantidad de droga inhalada redujo la incidencia de efectos secundarios. El uso de una solución bronco-dilatadora en la cual 0.4 por ciento de sulfato de isoproterenol fué combinado con 2.0 por ciento de fenilefrina no fué seguido en estas series de temblor ni de taquicardia.

Ninguna de las dos drogas causó cambio en la presión sanguínea en pacientes normo o hipertensos cuando fueron nebulizadas por este procedimiento.

RESUME

La phase gazeuse de dichlorodifluoromethane est bien tolérée et commode pour utilisation come propellant pour les aerosols bronchodilateurs. L'inhalation de cette gaz, en concentration d'environ quatre pour cent pare des malades avec du spasm des bronches ne produit pas de change en capacité vitale. Les effets secondaires de cette gaz aux concentrations basses sont minimaux et rencontrés rarement.

Les études des effets de l'inhalation de 0.5 pour cent de l'hydrochloride de isoproterenol et de 2.25 pour cent d'epinephrine racemic pare moyen

d'aérosolisation avec un appareil aérosolisateur activé par la phase gazeuse de dichloro-difluoromethane ont démontrées l'amélioration de la dyspnée et des augmentations attendantes de la capacité vitale. Les effets secondaires de ces bronchodilateurs sont minimales et consistent des tremeurs et de tachycardie. La réduction des quantités des bronchodilateurs inhalés cause l'élimination de ces effets secondaires. L'utilisation d'une solution de 0.4 pour cent de sulfate d'isoproterenol en combinaison avec 2 pour cent de phenylephrine ne produisaient aucune réaction secondaire. Aucune de ces bronchodilateurs produisaient des changes dans la pression artérielle ds sujets normaux ou hypertensive, lorsqu'ils étaient aerosolisés avec cet appareil d'aérosolisation.

ZUSAMMENFASSUNG

Dichlordifluoromethan in seiner Gas Form is ein gut tolerierter und leicht erhaltbarer Propellant für die Verstäubung der bronchodilatierenden Aerosols. Die Einatmung von 4% Dichlordifluoromethan in Patienten mit Asthma haben keinen Einfluss auf die Vital Kapazität. Nebenwirkungen mit Anwendung dieser niedrigen Mischungen waren minimal un wurden nur selten beobachtet.

Wenn 0.5% Isoproterenol oder 2.25% razamisches Epinephrin als Aerosol inhaliert wurden mit einem Gas-Phase Dischlorodifluoromethan betriebenen Versotäubungs Apparat wurden ausgezeichnete Erleichterung der Kurzatmigkeit und Erhöhung der Vital Kapazität beobachtet. Nebenwirkungen wurden selten befunden und bestanden aus Zittern und Herz Beschleunigung. Wenn etwas weniger von diesen Medikamenten inhaliert wurden verschwanden diese Nebenwirkungen. Eine Mischung von 0.4% Isoproterenol sulfat und 2.0% Phenylephrin, wenn inhaliert, was niemals von diesen Nebenwirkungen begleitet. Keines diese drei verschiedenen Medikamenten erhöht den Blutdruck normaler oder hypertensiver Patient-en, wenn inhaliert mit diesem Apparat.

REFERENCES

- 1 Barach, A. L.: "Physiologic Therapy in Respiratory Disease," J. B. Lippincott Co., Philadelphia, 1948.
- 2 Miller, W. F.: "A Consideration of Improved Methods of Nebulization Therapy," *Jour. Am. Med. Assn.*, 251:581, 1954.
- 3 Levine, E. R.: "Aerosol Therapy in the Management of Bronchopulmonary Infection Including Exsufflation;" in *Pulmonary Emphysema*; Editors: Barach, A. L. and Bickerman, H. A., Wilkins & Williams Co., Baltimore, 1956.
- 4 Unger, L. and Unger, A. M.: *J.A.M.A.*, 150:562, 1952.
- 5 Sayers, R. R., Yant, W. P., Chornyak, J. and Shoaf, H. W.: "Toxicity of Dichlorodifluoromethane: A New Refrigerant," *Report of Investigation of Dept. of Commerce, U.S. Bureau of Mines, R.I.*, 3013, May 1930.
- 6 Greenberg, L. and Lester, A.: "Acute and Chronic Toxicity of Some Halogenated Derivatives of Methane and Ethane," *Arch. Ind. Hyg. and Occ. Med.*, 2:335, 1950.
- 7 Dautrebande, L., Catry, D., Van Verkam, J. and Cereghetti, A.: "Essai de prevention Dela Silicase," *Union Miniere du Houst Katanga*, 1954 (Ref. 17).
- 8 Talbot, T. R., Jr., Quimby, E. H. and Barach, A. L.: "A Method of Determining the Site of Retention of Aerosols Within the Respiratory Tract of Man by the Use of Radioactive Sodium," *A.J.M.Sc.*, Dec. 1947.

- 9 Barach, A. L., Garthwaite, B. and Bickerman, H. A.: "Postgraduate Medicine," 5:314, 1949.
- 10 Abramson, H. A.: "Principles and Practice of Aerosol Therapy of the Lungs and Bronchi," *Ann. Allergy*, 4:440, 1946.
- 11 McKee, K. T. and Mosley: "The Use of Isuprel in the Treatment of Asthma," *J. So. Carolina Med. Assn.*, 46:72, 1950.
- 12 Cohen, E. N. and Van Bergen, F.: "Isuprel, A New Bronchodilating Agent," *Bull. Univ. Minn. Hosp.*, 19:424, 1948.
- 13 Gay, L. N. and Long, J. W.: "Council on Pharmacy and Chemistry," *Jour. A.M.A.*, 139:452, 1949.

General Anesthesia in Bronchoesophagology, A Review of Its Use in 4,000 Endoscopic Procedures Over a Ten Year Period

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It is well recognized that local anesthesia is used by most endoscopists on this continent and in England. It is the method of choice recommended in all text books dealing with bronchoesophagology and diseases of the chest;¹⁻⁶ Jackson and Jackson,¹ in 1934 stated, "General anesthesia is never used in our Clinic for endoscopic procedures." In recent years, however, with continuing improvements in methods and drugs used in general anesthesia, this method has gained some increase in favor, particularly in esophagoscopy and is even recommended for beginners in esophagology, by Jackson,² in 1950. Holinger⁷⁻⁸ also suggests its use in certain instances.

Although local anesthesia has proved to be extremely valuable in endoscopy it has limitations and dangers. Some of these have been referred to by Thomas and Fenton,⁹ Weisel and Tella,¹⁰ and Lierle.¹¹

While serving overseas in a 600 bed hospital, the author did bronchoscopies and esophagoscopies under local anesthesia, as previously taught and practiced. However, our anesthetist, the late Dr. A. St. C. Rumball,¹² was responsible for my initial interest in general anesthesia for endoscopic procedures. We used pentothal anesthesia (sodium thiopentone) many times, but as many others have found,¹³ we also observed that pentothal alone or in conjunction with local anesthesia was not satisfactory. We encountered many cases of laryngospasm and the patients had to be in a dangerously deep stage of anesthesia before they were sufficiently relaxed, particularly for bronchoscopies. We found that ether even without preliminary local gave excellent relaxation, but as these patients were all active, young, and usually healthy men, ether anesthesia was too time consuming in a busy military hospital. We eventually abandoned the idea, but happily fate brought us together again in Winnipeg, following hostilities, when we were both appointed to the staff of Deer Lodge Veterans' Hospital at the beginning of January, 1946. We eventually developed a method mutually satisfactory to both of us. The paper published by Casels and Holinger,⁷ in 1946 on "Points of Mutual Interest in Bronchology and Anesthesiology" brings back many fond memories and adequately describes our associations of that time. Our experience at Deer Lodge was confined to adults but at the same time the author was appointed to the staff of the Winnipeg General Hospital, and a little later to the Children's Hospital of Winnipeg, so that ample opportunity was provided to use

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general anesthesia for endoscopic procedures at all three hospitals, and I am very grateful to the anesthetists in all of these hospitals, who have been most cooperative and helpful, with useful suggestions and criticisms. More articles appeared in the literature,¹⁴⁻²³ describing the use of pentothal and curare, or allied relaxants. These were studied with interest and many of them appear in the bibliography.

Clinical Material

This review covers a period of approximately 10 years, from January 1946 to the end of September 1956 with personal records of 5,578 bronchoesophagological procedures, and of these 4,212 were carried out under general anesthesia. The remainder were done under local or without anesthesia, but are not considered in this review.

The choice of anesthetic depends on many factors, particularly the availability of an anesthetist and one that is willing and anxious to give anesthesia for endoscopy. It is also advantageous to have adequate recovery room space, and personnel to watch these patients until they have reacted sufficiently from the anesthetic. This has necessitated some changes in our plans and methods from time to time, since as is well known there is becoming a greater shortage of hospital space and it is not possible sometimes to observe the patients in a recovery room close to the operating room. When this condition arises we often use local anesthesia alone or with nisentil, to expedite the procedures and accommodate the hospital staff. It is not the intention to suggest that people who are familiar and satisfied with local anesthesia should change to general anesthesia. It is merely the purpose to present these cases that have been done under general anesthesia to illustrate that the method is as safe as local anesthesia alone.

The necessity of having an anesthetist who is interested and anxious to give anesthesia for endoscopy must be emphasized.

TABLE I
TOTAL PROCEDURES DURING A TEN-YEAR PERIOD (1946-1956)
CLASSIFIED AS TO YEAR, SEX AND TYPE

| Year | Number of Procedures | Male | Female | Bron- choscopy | Esopha- goscopy |
|-------|-------------------------|-------|--------|-------------------|--------------------|
| 1946 | 140 | 126 | 14 | 129 | 11 |
| 1947 | 343 | 295 | 48 | 300 | 43 |
| 1948 | 383 | 332 | 51 | 303 | 80 |
| 1949 | 425 | 336 | 89 | 313 | 112 |
| 1950 | 355 | 286 | 69 | 272 | 83 |
| 1951 | 442 | 319 | 123 | 317 | 125 |
| 1952 | 488 | 326 | 162 | 377 | 111 |
| 1953 | 493 | 343 | 150 | 382 | 111 |
| 1954 | 508 | 320 | 188 | 405 | 103 |
| 1955 | 364 | 206 | 158 | 293 | 71 |
| 1956 | 274 | 163 | 108 | 230 | 41 |
| TOTAL | 4,212 | 3,025 | 1,160 | 3,321 | 891 |

Table I illustrates the incidence according to year, sex and type of procedure. The ratio of three men to one woman is only partially explained by the fact that in a veterans' hospital most of the patients are men. Those done in the Veterans' Hospital constituted only about one-third of the total procedures. About one-quarter were esophagoscopies, the remainder bronchoscopies. In some cases both procedures were done, although these are not shown in the Table. In these cases the esophagoscopy is done first. Also, some patients have been done repeatedly. One girl who was 18 months old at the first bronchoscopy was done 25 times for the purpose of tracheal dilatation. One man had been bronchoscope 31 times under local, pentothal and curare.

Table II divides the cases into three age groups. This was done to show that a fair number of children were given general anesthetics. All of these children under 10 (450), were given ether alone, or in combination, except one child of eight who was bronchoscope under pentothal and flaxedil. The Table also illustrates that there were a considerable number of elderly people (386) over 70 years. The eldest receiving pentothal was 89 years. The largest group was from 10 to 69 years of age (3,376), and it was in this series that pentothal and curare gained prominence and proved to be most useful.

Preoperative Medication

Almost all patients were admitted to hospital the evening before operation, except emergency cases, particularly foreign bodies, which were done immediately. Adults were usually given barbiturate sedation the night before. Breakfast was withheld in the morning and all adults were given a hypodermic one hour preoperatively. At the Winnipeg General Hospital, morphine gr. $\frac{1}{8}$, gr. $\frac{1}{6}$ or gr. $\frac{1}{4}$ was given according to the usual methods of assessment. This is usually given along with atropine gr. 1/150. However if the individual is asthmatic or has many secretions that we wish to aspirate we do not give atropine. We also omit morphine

TABLE II
AGE DISTRIBUTION FOR THE TOTAL SERIES (4,212)

| Year | Under 10 Years | 10 - 69 Years | 70 Years and Over |
|-------|-------------------|---------------|----------------------|
| 1946 | 4 | 129 | 7 |
| 1947 | 3 | 323 | 17 |
| 1948 | 38 | 322 | 23 |
| 1949 | 52 | 338 | 35 |
| 1950 | 36 | 281 | 38 |
| 1951 | 35 | 348 | 59 |
| 1952 | 52 | 384 | 52 |
| 1953 | 56 | 393 | 44 |
| 1954 | 65 | 396 | 47 |
| 1955 | 56 | 268 | 40 |
| 1956 | 53 | 194 | 24 |
| TOTAL | 450 | 3,376 | 386 |

in asthmatics. At Deer Lodge Veteran's Hospital a combination of pantopon, gr. 1/3 and scopolamine gr. 1/150 is used one hour preoperatively. This dosage may be adjusted up or down as necessary. Infants are given no preoperative hypodermic. Children under 10 are sometimes given atropine preoperatively and occasionally a small dose of one of the barbiturates. Adrenalin by hypodermic, intravenous or rectal aminophyllin or hydrocortisone may be given to asthmatics preoperatively when indicated.

For a short period a barbiturate was given to adults two hours preoperatively but this was soon discontinued as it was felt that not only was it not necessary, but occasionally it made the patient too drowsy and it was felt that we had to keep some of these patients too long in the recovery room following pentothal in addition to the previously given oral barbiturate. Intravenous pentothal is an excellent antidote to any adverse reaction one may encounter from the topical agent.

Postoperatively we leave routine orders for nothing orally for two hours. However, usually by the time the patient has reacted from the general anesthetic it is safe for him to take water if he so desires.

Preliminary Topical Anesthesia

Almost all of our patients receiving pentothal first have topical anesthesia in the form of a spray and direct application by pledget into the pyriform fossae. These pledgets are wet enough to allow excess local to run into the larynx and therefore into the trachea. Occasionally if the mucosa appears sensitive we instill one cc. by cannula into the larynx. At Deer Lodge Hospital the anesthetic staff is partial to transtracheal local, and in this hospital after the patient has had the spray and applicators the anesthetist instills 1 or 2 cc.'s of the local by needle transtracheally. I personally feel that this is not necessary when one is using a

TABLE III
ANESTHETIC AGENTS EMPLOYED

| Year | Pentothal | Local and Pentothal | Pentothal and Curare | Local Pentothal and Curare* | Ether** |
|-------|-----------|---------------------|----------------------|-----------------------------|---------|
| 1946 | 5 | 16 | 76 | 38 | 5 |
| 1947 | 1 | 1 | 206 | 130 | 3 |
| 1948 | 1 | 6 | 90 | 248 | 38 |
| 1949 | 0 | 2 | 2 | 362 | 56 |
| 1950 | 1 | 2 | 1 | 296 | 54 |
| 1951 | 0 | 4 | 1 | 384 | 48 |
| 1952 | 2 | 0 | 2 | 446 | 60 |
| 1953 | 1 | 3 | 4 | 416 | 70 |
| 1954 | 3 | 17 | 0 | 390 | 98 |
| 1955 | 8 | 22 | 3 | 235 | 99 |
| 1956 | 12 | 45 | 0 | 142 | 85 |
| TOTAL | 34 | 118 | 385 | 3,087 | 616 |

*This includes Curare and Curare-like drugs. See Table IV.

**This includes Ether alone and in combination. See Table V.

general anesthetic. However we have had no ill effects from it, and I therefore do not object.

Type of Local Anesthesia.—To the end of January 1952, 2 per cent pontocaine (tetracaine) was used in the spray, and $\frac{1}{2}$ per cent pontocaine on the local applicators and for the intratracheal instillations. Cyclaine (hexyclaine) 5 per cent then became available and since February 6, 1952 we have used it almost exclusively. It appears to act more rapidly, is more effective. According to Orkin and Rovenstine,²⁴ it is safer than pontocaine.

Anesthetic Agents and Methods

Table III shows the trend by year of the different methods used. Pentothal was used only when the patient was old, debilitated, or extremely ill, where he objected to having a local spray or was known to have a sensitivity to local but where it was deemed advisable to have him asleep.

The second column in Table III shows that 118 cases were given local and pentothal only. Of these, sixteen were in 1946, when we were first starting to use curare and the number of cases again increased in 1954, 1955 and 1956. The reason for this is that we have found in some of our older patients, where we formerly used pentothal alone, we are now using local and just enough pentothal to have the patient asleep, and getting along well. Curare is not necessary in many of these elderly patients if preliminary local is used.

The third column in Table III shows our early attempts to use pentothal and curare without preliminary topical. This method was given a fair trial (206 times in 1947), but as stated previously larger quantities of pentothal and curare were required to achieve adequate relaxation, and consequently the reaction period following anesthesia was prolonged, and this method was therefore abandoned for the local, pentothal, curare combination.

Local Pentothal and Curare-like Drugs.—Table IV is a more detailed breakdown of the various types of muscle relaxants used in combination with local and pentothal. Curare is marketed by E. R. Squibb and Company under the name of Intocostrin, which is a purified extract of crude curare (purified chondodendrom tomentosum extract), and is packaged 20 units to the cc. We used this originally, and then later used d-Tubocurarine chloride, 3 mgm. to the cc. which is equivalent to 20 units of intocostrin. This is a pure substance and assayed by weight. In February 1952 we started to use flaxedil, tri (B-diethylaminoethoxyl) 1, 2, 3, benzene triodoethylate. This is synthetic curare marketed by Poulenc, Limited, 20 mgm. per cc. When succinylcholine chloride was marketed we first used it in 1952 under the trade name of anectine chloride, Burroughs Wellcome & Company, 20 mgm. to the cc. Succinylcholine is also marketed by Abbott under the trade name of Quelicin, and by Baxter under the name of rubilexin. When the anectine drip is referred to, a solution was made of 500 mgm. of succinylcholine in 500 cc.'s of 5 per cent glucose and saline.

Preferably we first apply the local as previously described. The 2½ per cent pentothal is then started intravenously and when the patient becomes unconscious the relaxant is injected separately into the tubing or the vein. We prefer curare or flaxedil; 1 or 2 cc.'s is given. We then wait two or three minutes and if further relaxation is required the relaxant is given in no greater quantity than 1 cc. at a time. If more pentothal is required, it too is given slowly. It is important that the pentothal and relaxant be kept in different syringes. Once the jaw is properly relaxed and the bronchoscope or esophagoscope is introduced we rarely require any more relaxant, just enough pentothal is used to keep the patient asleep or anesthetized only sufficiently for the endoscopist to continue his operation. Oxygen may be given continuously through the sidearm of the bronchoscope, and the concentration may be increased by closing the end of the bronchoscope with the thumb. We try to inform the anesthetist when we expect to be finished so that he will have the patient almost awake by the time the instrument is withdrawn.

Anectine 20 mgm. to the cc. in a syringe, and by the drip method was given a trial but we found that the margin of safety between proper relaxation and complete apnoea was too small. The actual dose by drip method was difficult to assess or control. On occasions we would have to withdraw the bronchoscope and either have to intubate or use oxygen by mask and bag to control respirations. In other words, although it is safe where the patient is previously intubated so that controlled respiration can be carried out, this is not practical where one requires to use the airway for the bronchoscope. Its use in esophagology was discontinued because it is rarely necessary to intubate a patient during esophagoscopy under pentothal or ether anesthesia. A large Roberts type esophagoscope is used and it is much easier to introduce if the patient does not have an endotracheal tube. Only occasionally, where pressure on the larynx may interfere with respiration, is intubation done and this is usually only necessary when one is working at the distal end of the esophagus.

TABLE IV
TYPE OF MUSCLE RELAXANT USED IN COMBINATION WITH LOCAL
AND PENTOTHAL IN 3,087 CASES

| Year | Curare | Flaxedil | Anectine | Anectine Drip |
|-------|--------|----------|----------|------------------|
| 1946 | 38 | | | |
| 1947 | 130 | | | |
| 1948 | 248 | | | |
| 1949 | 362 | | | |
| 1950 | 296 | | | |
| 1951 | 384 | | | |
| 1952 | 424 | 17 | 5 | |
| 1953 | 129 | 279 | 9 | 8 |
| 1954 | 50 | 305 | 12 | 23 |
| 1955 | 5 | 215 | 8 | 7 |
| 1956 | 0 | 140 | 1 | 1 |
| TOTAL | 2,057 | 956 | 35 | 39 |

Presently then we are using cyclaine 5 per cent topically, pentothal and flaxedil intravenously. It must be emphasized that these reagents are potent and must be used with great care. We have very occasionally encountered laryngospasm or bronchospasm postoperatively, but these are usually overcome with an oxygen mask or by lying the patient on his side or allowing him to sit up. If one waits for proper depth of anesthesia and relaxation before attempting to instrument the patient, laryngospasm will rarely if ever occur pre- or postoperatively. It has rarely been necessary to use curare antagonists,²⁵ prostigmine or tensilon chloride (edrophonium chloride) marketed by Hoffmann-La Roche, Inc. Asthma is a contraindication to the use of pentothal and curare and curare should be used sparingly, if at all in elderly and debilitated patients. It might also be reiterated that one must be on the lookout for myasthenia gravis where curare is of course contraindicated. Again we arbitrarily use 10 years of age as a minimum for the use of combined local pentothal and curare. Pentothal is not inflammable or explosive. It is an excellent antidote for any reactions one may get from the topical and in fact must reduce the incidence of such reactions.

To summarize then, curare or one of the curare like drugs was used in combination with local and pentothal in 3,087 procedures, and used in combination with pentothal but without local in 385 procedures. In this series there was one death, in June 1949. This was a 25 year old man who had been in the hospital almost continuously for three years with severe asthma. When first seen the morning of his death he had been in status asthmaticus and severe respiratory acidosis for two weeks. It appeared he had irreversible pulmonary damage and bronchoscopy was not done. Early that evening however at the insistence of his attending physician he was to have been bronchoscoped under ether which might have relieved his persistent bronchospasm. Unfortunately the anesthetist was not prepared to give ether and instead gave him 1.7 cc. of curare and 0.17 gm. of pentothal. Cardiac and respiratory arrest followed immediately and he could not be revived. Micropsy revealed over distended lungs and most of the small bronchioles were occluded with bronchiolar casts. Subsequently ether has been insisted upon in these cases and no operative death has occurred. Certainly if pentothal and curare or even local are to be used in a patient with history of asthma or who is having an asthmatic attack, one must be extremely cautious.

Ether

Ether still has an important place in bronchoesophagology. It is the only safe anesthetic for general anesthesia in infants. It is the anesthetic of choice in children under 10 years of age. The youngest in this series was five weeks old. It is also a safe anesthetic in elderly people. In the middle age group we use ether almost exclusively for asthmatics. Local is not necessary in these patients because adequate relaxation can be produced with ether alone. Although it takes a little more time and patience to anesthetize an adult asthmatic with ether, one does not run the risk of

TABLE V
TOTAL CASES IN WHICH ETHER WAS USED ALONE
OR WITH PENTOTHAL INDUCTION

| | |
|----------------------------------|-----|
| Ether Only | 465 |
| Ether and Rectal Pentothal | 116 |
| Ether and I.V. Pentothal | 22 |
| Ether, Local, and I.V. Pentothal | 3 |
| Ether and Local | 9 |
| Ether and Nitrous Oxide | 1 |
| TOTAL | 616 |

reaction to local. Table V illustrates the various ether combinations employed.

Ether and Pentothal.—Rectal pentothal was used as an induction agent in children 116 times. It is useful where the child is apprehensive or if the procedure is being repeated on many occasions. It may be given on the ward but preferably in the anesthetic room, and is followed with ether. We had a girl, 18 months old, with tracheal stenosis following intubation for acute laryngotracheobronchitis associated with measles. She was bronchoscoped a total of 25 times over a period of several years. She was always induced with rectal pentothal and then given ether by mask. She never had fear about the procedure. Likewise a boy, two years old, with severe stricture of the esophagus due to chemical burns was esophagoscoped and dilated directly through the esophagoscope 60 times in a period of seven years.

Ether and Intravenous Pentothal.—Rarely is induction done by pentothal intravenously in children. This method is usually reserved for adults who object strenuously to the smell of ether or prefer a needle to a mask. These people are sometimes given a small amount of pentothal intravenously and then continued with ether. Intravenous pentothal was used as the induction agent for only 22 procedures. In three of these local was also used. Ether and local alone were used in only nine cases, and in one case the child was induced with nitrous oxide.

Ether not only is the safest anesthetic for asthmatics, but it also benefits them therapeutically in that it produces relaxation of the bronchi and liquefaction of the secretions, thus allowing easier removal of secretions and bronchiolar casts.

Ether by its excellent relaxation of the larynx and cricopharyngeus also facilitates removal of foreign bodies from the tracheobronchial tree and esophagus in infants and children.

SUMMARY

This report includes 4,212 bronchoesophagological procedures under general anesthesia in a 10 year period.

Intravenous pentothal was given in 3,624 instances, and ether in 616.

Local anesthesia pentothal and a muscle relaxant (a curare-like drug) was the preferred method in adults. The relaxant drug was omitted in

some elderly and debilitated persons. Preoperatively morphine or pantopon was given, usually combined with atropine or scopolamine. Pontocaine was used as the topical agent until February 1952 after which time 5 per cent cyclaine was substituted. Flaxedil was also substituted for curare at this time.

Pentothal gives a pleasant induction, prevents and counteracts reactions from local agents, rarely produces postoperative nausea or vomiting, and if properly gauged the patient is usually reacting before leaving the operating room. It may be repeated many times without apprehension by the patient. It is not inflammable.

Pentothal and the relaxant must be given separately, induction must not be hurried and the patient must be at the proper depth of anesthesia and relaxation before attempting to introduce the endoscopic instrument.

Pentothal and curare are dangerous in asthmatics. The only death in this series occurred in an asthmatic person who had received these drugs.

Ether is the safest anesthetic for infants and was used routinely for children under ten. It is preferable in adults with severe emphysema, or asthma or tenaceous secretions. It may be used with pentothal as an induction agent either rectally or intravenously.

RESUMEN

Esta información corresponde a 4,212 maniobras broncoesofagológicas llevadas a cabo en diez años. En 3,624 se usó el pentotal intravenoso como anestésico general, y en 616 se usó del éter. Las drogas relajantes se omitieron en algunos ancianos y debilitados.

Preoperatoriamente se dieron morfina y pantopón, generalmente asociados a la atropina y la escopolamina. Se usó la pantocaína como tópicó hasta Febrero de 1952, y a partir de entonces se substituyó por la ciclaína al 5 por ciento. Se usó también desde entonces el Flaxedil en lugar del curare.

El pentotal proporciona una inducción agradable, evita y contrarresta las reacciones a los agentes locales, rara vez produce náusea postoperatoria o vómitos y si se dosifica bien, el enfermo ya reacciona antes de abandonar la sala de operaciones.

Puede usarse muchas veces sin que el paciente manifieste aprensión. No es inflamable.

El pentotal y el relajante deben darse por separado, la inducción no debe ser apresurada y el enfermo debe ser llevado a la profundidad de anestesia apropiada así como a la relajación, antes de introducir el instrumento endoscópico.

El pentotal con curare es peligroso en asmáticos. La única muerte en esta serie, ocurrió an un asmático que había recibido otras drogas.

El éter es el anestésico más seguro para los infantes y se usó como de rutina en los menores de diez años. Es de preferirse en los adultos con enfisema o asma o con secreciones muy espesas. Puede usarse con el pentotal como agente de inducción ya sea rectal o intravenosamente.

RESUME

L'auteur rapporte 4.212 examens broncho-oesophagologiques pratiqués sous anesthésie générale pendant une période de dix ans. Le pentothal intraveineux fut utilisé dans 3.624 cas, et l'éther dans 616 cas. On négligea la médication calmante chez certaines personnes âgées ou débilitées. Avant l'opération, on administra de la morphine ou du pantopon, généralement associé à de l'atropine ou à de la scopolamine. La pontocaine fut utilisée comme agent local jusqu'au mois de février 1952, date après laquelle la cyclaine à 5% lui fut substituée. Le flaxedil fut aussi substitué au curare à ce moment.

Le pentothal provoque un état agréable, empêche et combat les réactions des produits utilisés localement, produit rarement des nausées post-opératoires, ou des vomissements, et s'il est convenablement administré au malade, a généralement cessé son action avant que le malade ait quitté la salle d'opération. Il peut être répété plusieurs fois sans danger. Il n'est pas inflammable.

Le pentothal et les produits calmants doivent être donnés séparément, l'administration des produits doit se faire lentement, et le malade doit être suffisamment anesthésié et relaxé avant qu'on tente d'introduire l'instrument endoscopique.

Le pentothal et le curare sont dangereux chez les asthmatiques. Le seul décès dans ce groupe survint chez un asthmatique qui avait reçu d'autres médications.

L'éther est l'anesthésique le plus sûr chez les bébés, et il a été utilisé d'une façon habituelle chez les enfants de moins de dix ans. Il doit être préféré chez les adultes atteints d'emphysème sévère, d'asthme ou encombrés de sécrétions. Il peut être associé au pentothal, utilisé comme prémédication par voie rectale ou intraveineuse.

ZUSAMMENFASSUNG

Dieser Bericht hat zum Inhalt 4212 broncho-ösophageale Eingriffe unter Vollnarkose während einer Periode von 10 Jahren. Pentothal intravenös wurde in 3624 Fällen gegeben und 616 mal Äther. Das Relaxans wurde weggelassen bei einigen älteren und entkräfteten Personen. Vor dem Eingriff wurde Morphin oder Panthopon gegeben, gewöhnlich in Kombination mit Atropin oder Skopolamin. Pantocain wurde als Zeitgemässes Mittel gegeben bis Februar 1952 und danach ersetzt durch 5% Cyclamin. Zu dieser Zeit wurde auch das Curare durch Flaxedil ersetzt.

Pentothal liefert eine angenehme Narkose-Einleitung, verhindert und bekämpft Reaktionen örtlicher Wirkstoffe, führt selten zu postoperativem Schwindel oder Erbrechen, und bei richtiger Dosierung vermag der Patient bereits zu reagieren, ehe er den Operations-Saal verlässt. Es kann viele Male wiederholt werden ohne Abneigung des Kranken. Es ist nicht entzündbar.

Pentothal und das Relaxans müssen getrennt gegeben werden, die Einleitung der Narkose darf nicht überstürzt werden, und der Kranke muss

einen entsprechenden Grad von Schmerzunempfindlichkeit und Entspannung erreicht haben, ehe der Versuch der Einführung des endoskopischen Instrumentes unternommen wird.

Pentothal und Curare sind gefährlich bei Asthmatikern. Der einzige Todesfall in dieser Serie ereignete sich bei einem Asthmatiker, der andere Medikamente erhalten hatte.

Ather ist das sicherste Mittel Anaesthetikum bei Kindern und wurde routinemässig bei Kindern unter 10 Jahren benutzt. Es ist vorzuziehen bei Erwachsenen mit schwerem Emphysem oder Asthma oder zäher Sekretbildung. Es kann zusammen auf Pentothal zur Narkose-Einleitung gebraucht werden entweder rectal oder intravenös.

REFERENCES

- 1 Jackson, C. and Jackson, C. L.: *Bronchoscopy, Esophagoscopy and Gastroscopy*, 3d ed. W. B. Saunders Co., Philadelphia, 1934.
- 2 Jackson, C. and Jackson, C. L.: *Bronchoesophagology*. W. B. Saunders Co., Philadelphia, 1950.
- 3 Rubin, E. H. and Rubin, M.: *Diseases of the Chest*. W. B. Saunders Co., Philadelphia, 1947.
- 4 Benedict, E. R.: *Endoscopy*. The Williams and Wilkins Co., Baltimore, 1951.
- 5 Thomson, St. C. and Negis, V. E.: *Dis. Nose and Throat*, fifth ed. Appleton-Century-Crofts, Inc., New York.
- 6 Pullen, R. L.: *Pulmonary Diseases*. Lea and Febiger, Philadelphia, 1955.
- 7 Cassels, W. H. and Holinger, P. H.: "Points of Mutual Interest in Bronchology and Anesthesiology," *Ann. Otol., Rhinol. and Laryngol.*, 55:638, 1946.
- 8 Holinger, P. H.: "Progress in Esophagology," *Arch. Otol.*, 47:119, 1948.
- 9 Thomas, J. W. and Fenton, M. M.: "Fatalities and Constitutional Reactions Following the Use of Pontocaine," *Jour. Allerg.*, 14:145, 1943.
- 10 Lierle, D. M.: "Topical and Infiltration Anesthesia," *Transactions American Academy of Ophthalmology and Otolaryngology*, p. 288-293 (March-April), 1949.
- 11 Weisel, W. and Tella, R. A.: "Reaction of Tetracaine (Pontocaine) Used as Topical Anesthetic in Bronchoscopy, Study of 1,000 Cases," *J.A.M.A.*, 147:218, 1951.
- 12 Schoemperlen, C. B.: "Diagnostic Bronchoscopy," *C.M.A.J.*, 60:11, 1949.
- 13 Fatti, L. and Morton, H. J. V.: "Pentothal Anaesthesia in Bronchoscopy," *Lancet*, 1:597, 1944.
- 14 Lorhan, P. H. and Roberts, S.: "'Intocostrin'—Pentothal Sodium Anesthesia for Bronchoscopy and Laryngoscopy," *Arch. Otol.*, 46:789, 1947.
- 15 Adams, R. C.: "General Anesthesia," *Transactions American Academy of Ophthalmology and Otolaryngology*, p. 299-302 (March-April), 1949.
- 16 Pembleton, W. E. and Vinson, P. P.: "Anesthesia Peroral Endoscopy, Especially General Anesthesia in Esophagoscopy and Gastroscopy," *Arch. Otol.*, 50:561, 1949.
- 17 Butt, W. A. and Boys, H. W.: "Anaesthesia for Bronchoscopy and Oesophagoscopy," *Can. Med. Assoc. J.*, 60:62, 1949.
- 18 Scharfe, E. E.: "Anaesthesia for Peroral Endoscopy," *Can. Med. Assoc. J.*, 65:134, 1951.
- 19 Ament, R. and Meyers, H.: "Thiopental with Succinylcholine and Topically Applied Tetracaine. A More Ideal Anesthetic for Peroral Endoscopy," *A.M.A. Arch. Otol.*, 57:405, 1953.
- 20 MacIntosh, R. R.: "Anaesthesia for Bronchoscopy," *Anaesthesia*, 9:77, 1954.
- 21 Shane, S. M. and Ashman, H.: "A Method of General Anesthesia for Bronchoscopy and Bronchography," *Arch. Otol.*, 62:319, 1955.
- 22 Heatly, C. A.: "Practical Consideration of Anesthesia in Bronchoesophagology," *N. Y. St. J. Med.*, 56:367, 1956.
- 23 Tremble, G. E. and Baxter, J. A.: "Anaesthesia in Otolaryngology," *Can. Med. Assoc. J.*, 75:25, 1956.
- 24 Orkin, L. R. and Rovenstine, E. A.: "Topical Anesthesia with Hexylcaine (Cyclaine) for Major Endoscopic Procedures," *J.A.M.A.*, 160:1465, 1956.
- 25 Hunter, A. R.: "Antidotes to Curarizing Drugs," *Can. Med. Assoc. J.*, 74:892, 1956.

Blood Dyscrasias

Associated with Antituberculosis and Combined Antituberculosis-Tranquilizing Chemotherapy

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Introduction

The dynamics of chemotherapeutic drugs involve complex mechanisms in drug-parasite-host relationships. An increasing number of publications report severe blood dyscrasias induced by chlorpromazine and chloramphenicol, but few published reports incriminate antituberculosis drugs. Modern treatment of neuropsychiatric-tuberculous patients, including antituberculosis chemotherapy, surgical intervention, psychotherapy and tranquilizing drugs, has resulted in a gratifying picture on neuropsychiatric-tuberculosis wards. Arrest, inactivation, or removal of tuberculous lesions has been reflected in a dramatically improved neuropsychiatric condition in many patients. Prolonged antituberculous chemotherapy and the increasing use of tranquilizing drugs in treating neuropsychiatric and emotionally unstable tuberculous patients may cause serious problems.

The purpose of this publication is to report two cases (one a case of leukemoid reaction, hepatitis and dermatitis while on streptomycin and isoniazid, and the other a case of fatal agranulocytosis with confluent pleuropneumonia, on para-amino salicylic acid, isoniazid and chlorpromazine). Also to make a preliminary report of incidence of transient leucopenia, fluctuating leucocyte count and changes in differential count, based on clinical observation in cooperation with Dr. W. H. Newton.

Case 1: C. C. B. This 31 year old veteran was admitted to the neuropsychiatric-tuberculosis service, Veterans Administration Hospital, Downey, Illinois, on October 31, 1954. He had been continuously hospitalized elsewhere since 1949 for schizophrenic reaction, chronic, severe. Family History: Not remarkable. Past History: Syphilis, primary, in September 1944, treated; acute tonsillitis in December 1944; epididymitis, acute, non-venereal, in February 1945. The admission physical examination was within normal limits except for signs referable to the chest. X-ray films showed infiltration with cavitation in the upper lobe of the right lung and an infiltrate in the apical segment of the upper lobe of the left lung. Gastric washings contained acid fast bacilli on culture. The organisms were sensitive to streptomycin, para-amino-salicylic acid and isoniazid. Admission serology, hematology, blood chemistry and urinalysis were normal except for thymol turbidity test, 2 units.

On December 29, 1954 1 gram of streptomycin twice weekly, and 4 grams of para-amino salicylic acid three times daily, were started. Tranquilizing drugs were not given. Routine laboratory follow-up studies remained unchanged. On January 27, 1955, the 88th hospital day and 30th day of chemotherapy, he developed chills, fever of 103.4° F., nausea and malaise. Physical examination, except for moderate pharyngeal inflammation, was normal. Tetracycline, 1.0 gram daily, and penicillin, 600,000 units daily, were given but a remittent type of fever spiking to 104.4° F. persisted and he became increasingly toxic. On February 7, 1955, 12 days after onset of this acute episode, he reacted with increased nausea, emesis and pain in the right upper abdominal quadrant. Other new signs included mild swelling of the soft tissues of the orbit bilaterally, generalized erythematous dermatitis, generalized lymphadenopathy, and palpable, tender liver. The pharynx remained unchanged. The lack of response to broad spectrum antibiotics, sterile cultures for B hemolytic streptococci, the clinical

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picture and laboratory findings were all considered compatible with hypersensitivity reaction due to drugs. Therefore, SM and PAS were stopped. Slowly decreasing temperature followed. However, he appeared more toxic. Tetracycline and penicillin were discontinued on the following day but low grade fever without spiking continued. On February 8, 1955 icterus was noted in the sclerae. Laboratory findings that day were: Urinalysis—albumin 3+, urobilinogen quantitative 1:160 dilution. Hemogram—white blood cell count 25,000, 80 per cent neutrophils, 18 per cent lymphocytes, and 2 per cent eosinophils, red blood cell count 3,780,000, hemoglobin 12 grams, color index 1.02, mild basophilic stippling, malaria negative, sedimentation rate 3 mm. per hour, icteric index 44.2 units. Cephalin flocculation was 3+ in 48 hours, thymol turbidity 6.25 units, fasting blood sugar 106 mg. per cent, NPN and urea nitrogen not elevated.

Liver function tests and urinalysis showed marked hepatocellular impairment. On February 11, 1955, the hemogram showed WBC 95,000 24 per cent neutrophils, 39 per cent lymphocytes, 29 per cent eosinophils, 8 per cent monocytes, a blood picture resembling a leukemoid reaction with enlarged lymphocytes. This report was re-checked and confirmed by the chief of the laboratory service, Dr. M. A. Jacobson. Bone marrow examination, the electrophoretic protein pattern, and other immunochemical studies were requested but were not available at the time.

The initial leucocytosis with 80 per cent neutrophils was considered a response to tissue damage, the subsequent lymphocytosis as a lymphoid or reticuloendothelial tissue response, and eosinophilia was compatible with an allergic state, giving a clinical picture strongly suggestive of reduction in circulating antibodies. Empirically he was given 0.15 cc. per kilo of gamma globulin intramuscularly. The next day he appeared less toxic and subsequently improved slowly. Infectious mononucleosis was considered as an alternate explanation of the rather bizarre sequence of events. Heterophile antibody test of Paul-Bunnell was reported positive in 1:28 dilution on February 14, 1955, in 1:56 dilution on February 16, 1955, but was negative on February 25, 1955. This diagnosis, therefore, was not proved.

Hemogram on February 14, 1955 showed white blood cell count 28,000, 69 per cent lymphocytes, 31 per cent neutrophils. ECG on February 15, 1955 was read as normal. A small test dose of 250 mg. streptomycin resulted in reaction consisting of chills, fever and skin rash. A test dose of 3 grams of rezipas resulted in nausea, malaise, leucocytosis and slightly abnormal liver function tests. On April 18, 1955 the total protein was 8.24, A/G ratio .585, A/B ratio 3.10, albumin 36.90 per cent, alpha 1, 6.03 per cent, alpha 2, 9.30 per cent, beta 11.90, gamma globulin 35.82 per cent.

The anti-streptolysin titer was 1:500 on February 25, 1955. On recheck April 18, 1955 by the Naval Medical Research Laboratory, Great Lakes, Illinois, the anti-streptolysin titer was 1:600. These findings do not necessarily incriminate the streptococcus as a direct etiologic agent and may have indicated previous streptococcal infection.

Since February 15, 1955 symptoms, signs and laboratory reports have shown steady improvement. He became asymptomatic and by the end of May all laboratory findings returned essentially to normal values. Following recovery there was no radiologic evidence of progression of the bilateral tuberculous lesions. Antituberculosis chemotherapy consisting of INH alone was restarted on September 14, 1955, with slowly increasing doses to 100 mg. three times daily by September 26, 1955. Pyrazinamide, 1.5 grams daily, was added April 10, 1956 without untoward reaction and has been continued. Viomycin was tried but caused recurrence of fever, malaise and leucocytosis. The right upper lobe was resected on May 15, 1956, when penicillin and tetracycline were tolerated without difficulty. His postoperative course was protracted, the remaining lobes expanding slowly and with gradual absorption of fluid. Following surgery cultures were negative for acid fast bacilli until recently. Planigraphic studies show evidence of possible cavitation in the left upper lobe. The tubercle bacilli are sensitive to SM, PAS and INH. Segmental resection on the left side is being considered.

Case 2: J. D., This 30 year old white single man, was admitted to the neuropsychiatric-tuberculosis service, Veterans Administration Hospital, Downey, by transfer from Fitzsimons Army Hospital September 30, 1955. He had first been hospitalized at Camp Gordon on January 3, 1955 for an acute psychiatric disorder. Routine chest x-ray film showed an infiltrate in the left apical region and he was transferred to Fitzsimons on February 11, where he reacted to tuberculin but not to coccidioidin and histoplasmin. Three gastric cultures were negative for acidfast bacilli. He had been given SM, 1 gram every third day, and INH, 300 mg. daily. In addition he had received 30 electroshock treatments, from February 8 to March 30, 1955, and 33 insulin shock treatments, from April 13 to May 27, with some improvement in his mental condition.

On admission to the hospital the physical examination was within normal limits. His height was 72", weight 149 pounds, blood pressure 118/78. Because of mental confusion, it was difficult to obtain a clear picture of his past and family history other than that he had come to the United States from Yugoslavia after the second world war.

Hospital Course: Antituberculosis chemotherapy consisting of SM, 1 gram twice weekly, and INH, 300 mg. daily, was continued until December 1955, when he refused SM injections and the regimen was changed to PAS, 12 grams daily, and INH, 300 mg. daily. Serology, blood chemistry and urinalysis were normal. The white blood cell count was 5,200, with 65 per cent neutrophils, 33 per cent lymphocytes, 2 per cent monocytes. The hemoglobin was 14.5 grams, color index 1.0, sedimentation rate 1 mm. per hour. Liver function tests on October 4, 1955 showed cephalin flocculation 2+ in 48 hours, thymol turbidity 3.00 units. BSP test on January 4, 1956 showed 1.0 per cent retention in 45 minutes. The pulmonary condition was evaluated at the medical staff conference and on February 20, 1956 the diagnosis of tuberculosis, pulmonary, chronic, minimal, active, was changed to minimal, active, improved.

On December 6, 1955 he was placed on chlorpromazine, 50 mg. twice daily. On May 7, 1956 he eloped from the recreation room and subsequent to his return became an eating problem. In two weeks he lost six pounds of body weight and, therefore, supplemental tube feeding was started. On May 15, 1956 cephalin flocculation was 2+ in 48 hours, thymol turbidity 1.5 units. Hemogram on May 16, 1956 showed 6,800 white blood cells with 61 per cent neutrophils, 39 per cent lymphocytes, hemoglobin 14 grams 91 per cent, color index 0.96, sedimentation rate 4 mm. per hour.

On May 28, 1956 at 2:30 P.M. after 200 cc. of supplemental nourishment had been given, he had emesis. Tube feeding was stopped, and no side effect was noted the remainder of the day. His temperature was 98° F. orally, pulse 86, respiration 18, blood pressure 100/74, with no coughing spells. On May 29, 1956 at 8 a.m. he appeared acutely ill, with abrupt onset of chills, pounding pulse 114, temperature 102.6° F., respiration 28, blood pressure 110/70. The mouth and throat showed slight congestion but no ulceration. There were suppressed breath sounds over the lower half of the right lung and, after a few hours, fine rales were heard and impaired percussion elicited. He developed non-productive painful coughing spells but no other symptom or sign. Emergency leucocyte and differential count revealed 1,250 white blood cells with 25 per cent neutrophils, 68 per cent lymphocytes, 7 per cent monocytes. Sputum for bacteriologic studies could not be secured. Portable chest x-ray film showed pneumonic infiltration in the right lower lung field. Our clinical impression was (1) granulocytopenia due to drug hypersensitivity, (2) right lower lobe pneumonia, probably from inspiration of vomitus on previous day. Chlorpromazine, PAS and INH were discontinued and, in order to combat what appeared to be severe pulmonary infection, crystallin, 600,000 units q 12 hours, and tetracycline, initial dose 500 mg. with 250 mg. q 4 hours were started. Liver extract, 20 mg. USP 1 q 12 hours, was given in the hope of stimulating the bone marrow. His temperature rose gradually to 104.2° F. At 9 p.m. his pulse was 126, respiration 30. At 10:30 p.m. his temperature was 105.2° F. and he developed signs of hypotension with dyspnea, cyanosis and repeated emesis. However, he was able to take fluids and liquid nourishment orally until the end. Symptoms and signs of circulatory failure attributed to bacterial toxemia were progressive. On May 30, 1956 at 7:30 a.m. oxygen was started. By 8:30 his temperature was 106°, followed by a rapid drop, Cheyne-Stokes respiration and vascular collapse. He expired at 9:05 a.m.

Necropsy revealed moderate fibrosis with a large number of congested blood vessels resembling an angiomatous pattern in the apex of the lung. Large areas of extravasated blood were also present. Small accumulations of lymphocytes were seen. The adjacent alveolar tissue contained edema fluid with large numbers of bacteria. *Other areas of the lung* disclosed a pneumonia-like appearance. The alveoli were filled with round cells, only a few of which were polymorphonuclear leukocytes, others resembled histiocytes. Many cells of the exudate revealed coarse granula in their cytoplasm. Red blood cells were also present in the alveolar spaces, variable in size and with a more bluish appearance in contrast with the erythrocytes inside blood vessels. The alveolar wall as well as the other lung tissue did not stain normally and had an appearance resembling that found in infarcted areas (Figures 1A, 1B). Small fat droplets were seen in the liver cells, but there was no other finding indicating toxic damage. There was moderate passive congestion of spleen pulpa, no finding indicating increased hemolysis. Moderate passive congestion was present in the kidneys and occasional minimal transudation in Bowman's capsules. The

heart, adrenals, prostate and brain showed no histopathological change. Bone marrow smear showed degeneration of myeloid cells while myeloblasts were aplastic.

Comment

Other published reports and our case of leukemoid reaction have presented various bizarre features. Attempts to explain the mechanism of leukemoid reactions have led to the following theories: (1) Stimulation of the bone marrow, (2) Antigen-antibody reaction, (3) Infection, or (4) Mechanically by ectopic hemopoieses secondary to prolonged demand on the blood-forming organs.

In our case of leukemoid reaction with hepatitis and dermatitis, we feel that both streptomycin and PAS were injurious to the blood-forming organs. Attempts to resume treatment with the incriminated drugs were unsuccessful because of the patient's intolerance. His reaction to viomycin may be explained by cross-reaction. We regret giving gamma globulin empirically without awaiting results of the electro-phoretic protein pattern, bone marrow and lymph node biopsy studies, but the toxic condition and resulting improvement may justify our decision.

In the case, granulocytopenia with secondary confluent pleuropneumonia, all three drugs (chlorpromazine, para amino salicylic acid and isoniazid) may be implicated. Because of the rapidly progressive course of only 26 hours, it could not be determined which drug caused the irreversible damage in the bone marrow. Experimental granulocytopenia in varying degrees has been produced with the use of antileucocytic serum in vitro and in vivo (S. Moeschlin, H. Myer, L. G. Israels and E. Tarr). The presence of leucoagglutinins in serum of leucopenic patients has been reported

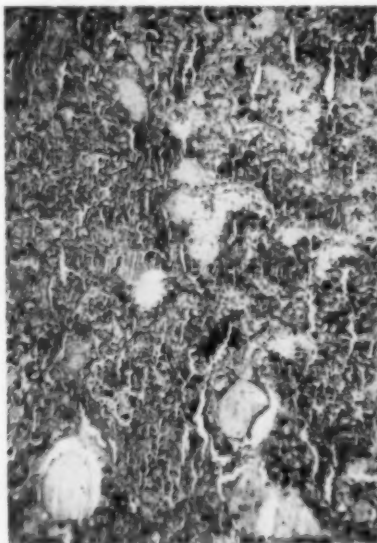


FIGURE 1A

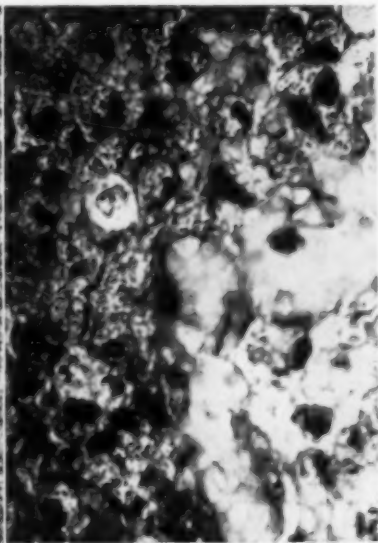


FIGURE 1B

with fatal outcome. Probably they are antibodies acting on antigens carried by human leucocytes. Results of more recent studies imply that leucopenia is produced by agglutination of leucocytes in peripheral circulation with subsequent removal of leucocytes in the lung capillaries.

The anaphylactoid course of pulmonary infection and failure of penicillin, 600,000 units every 12 hours with tetracycline, resulted because of the

INCIDENCE OF MILD FLUCTUATING BLOOD REACTION, Patients at VA Hospital, Downey, Illinois, Neuropsychiatric-Tuberculosis Service (251 bed capacity) during 1956.

| | |
|---|-----|
| Patients treated (total) | 337 |
| Patients receiving anti-tuberculous or tranquilizing drugs, or both | 229 |
| Total incidence, aberrant blood findings (excluding surgical cases, transient illnesses, and two cases with severe reactions, described elsewhere in this report) | 55 |
| Leukopenia (below 5,000 WBC) | 17 |
| Leukocytosis (above 10,000) | 30 |
| Reversed neutrophil-lymphocyte differential count | 8 |
| Returned to normal, one to four weeks, following drug discontinuance | 55 |

TABLE I
LEUKOPENIA FINDINGS—17 CASES

| DRUG REGIMENS | | | | LABORATORY FINDINGS | | | | SYSTEMIC |
|-------------------------|-----------------|--------------------------------|-----------|---------------------------|-----------------------|----------------|-----------------------|---|
| At time of reaction | | | | Prior | At Time | | | |
| Anti-TB (Mos. prior) | | Tranquillizing (Mos. prior) | | Cephalin floc. 48 hrs. | Thymol turb. units | Cephalin floc. | Thymol turb. units | Temp. elevation Dermatitis GI symptoms Dyspnea |
| 2 | SM-PAS | 33 | Frenquel | 12 | 1+ | 3.5 | 0* | 0* |
| | | 19 | | 5 | 2+ | 3.5 | 1 | 2 |
| 1 | SM-INH | 24 | Serpasil | 17 | 0 | 0 | 1+ | 1.5 |
| 1 | SM-INH | 20 | Thorazine | 10 | 0 | 0 | 1+ | .5 |
| 4 | SM-INH | 17 | None | 0 | 1.5 | 0 | 1.5 | |
| | | 2 | | 4+ | 3.5 | 0 | 3.0 | |
| | | 42 | | 0 | 1.74 | 0 | 2.5 | |
| | | 39 | | 0 | 2.5 | 0 | 2.5 | |
| | | | | | | | | dermatitis (SM) |
| 1 | SM-PAS & INH | 4 | Sparine | 3 | 2+ | 1.5 | trace | 1.5 |
| | | | | | | | | severe dermatitis |
| 2 | SM-PAS & INH | 19 | | 5 | 1+ | 2.0 | 0* | 0* |
| | | | | | trace | .2 | 1+ | 2.82 |
| 1 | PZA-INH | 4 | Sparine | 3 | 0 | 1.5 | 0 | 1.5 |
| 1 | SM | 1 | None | | 2+ | 2.0 | 1+ | 2.5 |
| 1 | None | | Atarax | 2 | unknown | unk. | 3+ | 3.5 |
| 1 | None | | Thorazine | 11 | Icteric index | 6.5U | unk. | unk. |
| 1 | None | | None | | 0 | 2.5 | unk. | unk. |
| 1 | SM-INH | 9 | Frenquel | 8 | 0 | 0 | 4+ | 5.37 |
| | | | | | | | | hepatitis, with icterus |

*Temporarily negative only.

inability of the body to mobilize its defenses, a sequel of the destruction of the leucocytes, essential elements in the body's defensive mechanisms. The often reported beneficial effect of the combined use of ACTH or cortisone in addition to the antituberculosis drugs in severe infections and drug-hypersensitivity reactions in suppressing not only fever but neutrophilia was not justified in our case in patient with pulmonary tuberculosis without coverage of antituberculosis drugs. Whether blood transfusion, which was planned for the next day, would have helped to correct the circulatory failure seems doubtful.

For reported incidence of transient, mild, fluctuating blood dyscrasias, leucopenia, shift in differential count and leucocytosis among our neuropsychiatric patients (see Table I). The clinical observations were undertaken with the purpose of watching for signs of early mild reactions, in order to prevent the development of more severe toxic blood dyscrasias. The preliminary impression, based on current clinical observations, does not implicate specifically one single or combination of drugs for increased incidence. The observed fluctuation of the blood picture may be explained in the light of present concepts by enzymatic interference of most of the drugs in drug-parasite-host relationships. Immediate discontinuation of the offending drug or drugs brought reversal of the abnormal blood picture in one to four weeks. The greater incidence of mild blood dyscrasias among our patients who are on chemotherapy may be understood by (1) the older age distribution of our patients, 73 per cent of whom are over 50, and 60 per cent over 60 years of age, (2) the long period of hospitalization for neuropsychiatric conditions, tuberculosis, or both, (3) coexisting organic diseases such as chronic alcoholism with liver damage, (4) various previous drug regimens, insulin coma or electroconvulsive therapy. We have no reason to believe that neuropsychiatric-tuberculous patients, as such, are constitutionally more susceptible to adverse drug reactions than other patients with tuberculosis.

It appears of interest to note that in some cases, when the suspected drug or drugs were resumed with supplemental vitamins as indicated, the blood picture remained normal, other side effects such as skin rashes and gastric intolerance disappeared, and well-being improved. These observations are in agreement that most chemotherapeutic agents may be considered antimetabolites. Our clinical observations for evaluating supplemental use of vitamins to correct a clinically suspected deficiency have been favorable and in accord with published results elsewhere.

SUMMARY

Two cases of hypersensitivity reaction to antituberculosis drugs are reported. With streptomycin and para-amino salicylic acid, one presented spiking fever, generalized erythematous dermatitis, lymphadenopathy, hepatitis with icterus, and a blood picture resembling infectious mononucleosis with leukemoid-lymphocytic reaction. Following desensitizing doses of streptomycin and PAS, the patient again showed evidence of toxicity to these drugs and also apparent cross-reaction with viomycin.

He tolerated isoniazid, pyrazinamide, and the broad-spectrum antibiotics.

The other with PAS, isoniazid and chlorpromazine developed granulocytopenia, pleuropneumonia, and rapidly progressive circulatory failure attributed to bacterial toxemia, with no response to combined broad-spectrum antibiotics. The responsible drug or drugs could not be determined because of the rapidly fatal termination 26 hours after the onset of the acute illness.

Preliminary clinical observation does not specifically implicate one single or combination of drugs. Our clinical experience in the evaluation of the supplemental use of vitamins in correcting clinically suspected deficiencies has been favorable when a drug suspected of causing toxicity was resumed and apparently well tolerated.

RESUMEN

Se relatan dos casos de hipersensibilidad a las drogas antituberculosas. El primer enfermo, tratado con estreptomycin y PAS presenta un extraño cuadro clínico caracterizado por fiebre en agujas, dermatitis eritematosa diseminada, linfadenopatía, hepatitis icterica y fórmula sanguínea parecida a la mononucleosis infecciosa con reacción leucemoide-linfocítica. Después de tratarse con dosis desensibilizantes de estreptomycin y PAS el enfermo mostró nuevamente evidencias de toxicidad a esas drogas así como reacción cruzada aparente a la viomicina. Tolera isoniácida, pirazinamida y los antibióticos de amplio espectro.

El segundo caso fué tratado con PAS, isoniácida y chlorpromazina. La toxicidad se manifestó por una reacción anafilactoide con principio repentino de granulocitopenia, pleuroneumonía, y desfallecimiento progresivo y rápido circulatorio atribuido a toxemia bacteriana sin res puesta a los antibióticos de amplio espectro. No se pudo determinar cual era la droga o las drogas responsables debido a la terminación fatal después de 26 horas del principio de la enfermedad aguda.

La frecuencia de discrasias sanguíneas moderadas aparentes, entre los enfermos neuropsiquiátricos tratados por drogas antituberculosas así como drogas tranquilizantes durante el año pasado, es objeto de información. La variación al aparecer mayor de fluctuaciones en los cuadros sanguíneos en 54 enfermos de un total de 229 bajo varios regímenes de drogas puede explicarse tal vez por: (1) edad mayor de los trastornos orgánicos coexistentes, (2) tratamiento prolongado con tales procedimientos o como el coma insulínico y los electrochoques. Las observaciones clínicas preliminares no implican de manera especial a una simple droga o combinación de drogas. Nuestra experiencia clínica en la valuación de las vitaminas para corregir las deficiencias sospechadas clínicamente ha sido favorable cuando la droga sospechosa de toxicidad se ha vuelto a emplear y es entonces bien tolerada. Esto está de acuerdo con otras informaciones antes publicadas.

Los resultados de los estudios publicados recientemente para aclarar los mecanismos fundamentales de las dicrasias sanguíneas causadas por las drogas antituberculosas, las tranquilizantes o las combinaciones se discuten aquí y se recalca la necesidad de hacer una estimación cuida dosa

de la dinámica se las relaciones droga parásito-huésped antes de usar las drogas. La posibilidad de efectos desagradables complicando la quimioterapia en los individuos susceptibles, se hace resaltar.

RESUME

L'auteur rapporte deux cas d'hypersensibilité aux médicaments antituberculeux. Le premier malade, traité par la streptomycine et le P.A.S. présente une évolution clinique bizarre, caractérisée par une fièvre hectique, une dermatite érythémateuse généralisée, des adénopathies, une hépatite avec ictère, et une atteinte sanguine ressemblant à une mononucléose avec réaction lymphocytaire leucémoïde. Après essai de désensibilisation à la streptomycine et au P.A.S., le malade donna de nouveau la preuve d'une intoxication due à ces médicaments et manifesta en outre une réaction croisée évidente à la viomycine. Il toléra l'isoniazide, la pyrazinamide et les antibiotiques de seconde zone.

Le deuxième cas fut traité par le P.A.S., l'isoniazide, et la chlorpromazine. La toxicité manifestée était de type anaphylactique caractérisée par une apparition soudaine d'agranulocytose, de pleuropneumonie, et une atteinte circulatoire progressive, attribuée à la toxémie bactérienne, qui ne répondit pas aux associations d'antibiotiques mineurs. La ou les médicaments responsables ne purent être précisés à cause de la rapidité de l'évolution qui se montra fatale 26 heures après l'apparition des manifestations.

L'auteur rapporte l'apparition de manifestations sanguines, faibles et transitoires chez les malades de neuropsychiatrie, traités par les médicaments antituberculeux et calmantes au cours de l'année. La fréquence de fluctuation apparemment plus grande dans les tableaux sanguins de 54 malades sur un total de 229 malades soumis à des régimes médicamenteux différents, peut être expliquée par 1) l'ancienneté des troubles organiques coexistants; 2) un traitement prolongé associé à des moyens tels que le coma insulinaire, et la thérapeutique électroconvulsive.

ZUSAMMENFASSUNG

Bericht über 2 Fälle von Überempfindlichkeits-Reaktion gegen antituberkulöse Heilmittel.

Der 1. Patient wurde mit Streptomycin und PAS behandelt und bietet einen bizarren klinischen Verlauf, charakterisiert durch zackenförmigen Fieberverlauf, generalisierte erythematöse Dermatitis, Lymphadenopathie, Hepatitis mit Gelbsucht und einem Blutbild, ähnlich der infektiösen Mononukleose mit leukaemisch-lymphozytärer Reaktion. Im Anschluß an desensibilisierender Dosen von Streptomycin und PAS bietet der Patient wieder das Bild der Toxizität auf dieses Medikament, so wie auch eine augenscheinliche Überkreuzreaktion mit Viomycin. Er vertrug INH, Pyrazinamid und die Breitwandspektrum Antibiotika.

Der 2. Fall wurde behandelt mit PAS, INH und Chlorpromacin. Seine Toxizität manifestierte sich als ein anaphylaktischer Reaktionstyp gekennzeichnet durch plötzliches Auftreten einer Granulocytopenie, Pleuropneumonie und rasch fortschreitendes Kreislaufsversagen als Ausdruck

bakterieller Toxämie mit fehlender Antwort auf kombinierte Breitwand-spektrum Antibiotika. Das oder die verantwortlichen Heilmittel konnten nicht ermittelt werden wegen des raschen tödlichen Ablaufes 26 Stunden nach dem Beginn der akuten Erkrankung.

Bericht über das Auftreten von offenbar flüchtiger, leichter Dyscrasie des Blutes unter neuropsychiatrischen Patienten während der Behandlung mit antituberkulösen sowie mit beruhigend wirkenden Arzneimitteln im Verlauf des vergangenen Jahres. Die scheinbar grössere Häufigkeit des Schwankens des Blutbildes bei 54 Kranken von insgesamt 229 Kranken unter verschiedenen Arzneimittelkombinationen kann erklärt werden 1) durch die erhöhte Altersverteilung gleichzeitig vorkommender organischer Störungen, 2) durch die verlängerte Behandlung kombiniert mit Insulin-, Koma-, Elektro-Schockbehandlung. Die bisherige klinische Beobachtung lässt kein einzelnes Medikament oder eine Medikamenten-Kombination besonders beteiligt sein. Unsere klinische Erfahrung bei der Auswertung der ergänzenden Anwendung von Vitaminen zur Korrektur klinisch vermuteter Mangelercheinungen waren günstig, wenn ein Medikament, dessen toxische Wirkung vermutet wurde, wieder verordnet und augenscheinlich gut vertragen wurde. Dies stimmt überein mit früher veröffentlichten Berichten.

Besprechung der Resultate der neueren Literatur über Untersuchungen zur Aufklärung der grundlegenden Mechanismen der Blutzersetzung entstanden durch Antituberkulöse Mittel, Beruhigungsmittel oder kombinierte Chemotherapie; hervorgehoben wird die Notwendigkeit vorsichtiger Erfassung des Kräftespieles in der Beziehung zwischen Medikament, Erreger und Wirt. Betont wird die Möglichkeit ungünstigen, komplizierender Wirkungen der Chemotherapie bei empfindlichen Individuen.

BIBLIOGRAPHY

- Dausset, J. and Menna, A.: "Presence of Leucoagglutinins in Serum of Three Leukopenic Patients," *Sang. Paris*, 24:410, 1953.
- Moeschlin, S., Meyer, H., Israels, L. G. and Tarr, G. E.: "Experimental Agranulocytosis," *Acta Haemat.*, 11:73, 1954.
- Dameshek, W.: "Hemotoxic Reactions to Drugs," *Postgraduate Medicine*, 16:369, 1954.
- Schwartz, R. S. and Hass, W. K.: "Leucoagglutinins in Agranulocytosis," *A.M.A. Arch. Med.*, 95:863, 1955.
- Mahrer, R. A. and Maret, R.: "Agranulocytosis Complicating PAS and Streptomycin Therapy," *U. S. Armed Forces M. J.*, 6:1193, 1955.
- Hilts, S. V. and Shaw, C. C.: "Leukemoid Blood Reactions," *New England J. Med.*, 249:434, 1953.
- Friedman, E.: "Reactions to Para-Amino Salicylic Acid," *Am. Rev. Tuberc.*, 72:833, 1955.
- Lichtenstein, M. R. and Cannemeyer, W.: "Severe Para-Amino Salicylic Acid Hypersensitivity Simulating Mononucleosis or Hepatitis," *J.A.M.A.*, 152:606, 1953.
- Steininger, W. J., Klopfenstein, M. D. and Woodruff, C. E.: "Fatal Allergic Reaction to Para-Amino Salicylic Acid," *Am. Rev. Tuberc.*, 69:451, 1954.
- Biehl, J. P. and Nimitz, H. J.: "Studies on the Use of a High Dose of Isoniazid," *Am. Rev. Tuberc.*, 70:430, 1954.
- Hall, W. H. and Gold, D.: "Shock Associated with Bacteremia," *A.M.A. Arch. Int. Med.*, 96:403, 1955.
- Hansen, J. E. and Cleve, E. A.: "Fatal Hypersensitivity to PAS and Streptomycin," *Dis. Chest*, 28:577, 1955.
- Bulley, K. G.: "Near-Fatal Shock From PAS Followed by Guillain-Barres Syndrome," *Am. Rev. Tuberc.*, 69:455, 1954.

SECTION ON CARDIOVASCULAR DISEASES

Experiences with Myocardial Revascularization By Division of the Internal Mammary Arteries

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Coronary arterial disease holds the dubious distinction of being the major cause of death and disability in the field of cardiac disorders. Its prevalence seems paradoxically to be increasing despite mounting efforts to modify its ravaging but insidious course. Basically, the offending lesion is that of arteriosclerotic vascular degeneration with its resultant gradual or sudden occlusion of portions of the arterial tree depriving the myocardium of its only source of sustenance. Although inroads have been made toward the modification of this sclerotic process by metabolic means, the ultimate solution seems remote at the moment. In the interim both physician and surgeon have attempted to improve myocardial vascularity, despite the natural progression of occlusive changes, by augmenting its diminished blood supply from neighboring vascular structures or by redistribution of myocardial blood from unaffected to affected areas.

In 1939 at the suggestion of Fieschi¹ in Italy, Zoja and Cesa-Bianchi ligated the internal mammary arteries of a patient who for some years had suffered from repeated myocardial infarcts. The operation was performed under local anesthesia and the patient enjoyed an excellent postoperative course. To quote Fieschi—"The patient, after two years, is still alive and has had no further acute attacks of infarction." This operation was the culmination of Fieschi's rather modest attempts to amplify known anatomic demonstrations of the naturally occurring communications found between the ramifications of the internal mammary arterial bed and the coronary circulation. Previously he had been able to trace, by radio-opaque injections, vascular channels from the internal mammary artery through its pericardiophrenic branch into a few periaortic and peripulmonary arterial rami. It was his hypothesis that the coronary arterial circulation

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might be favorably influenced by creating hypertension in the circulatory collateral of the mammary arteries by occluding these vessels in the second intercostal space. Indifference on the part of his professional contemporaries prevented expansion of this effort just as similar apathy has impeded the enthusiasm of most investigators throughout the world regardless of their field of endeavor.

In 1955, Battezzati, Tagliaferro and DeMarchi¹ amplified the work of Fieschi and reported the results of their anatomico-surgical research both experimental and clinical. In cadavers they injected methylene blue and India ink at the level of the second intercostal space into a segment of the internal mammary artery containing the origin of the pericardio-phrenic artery after occlusion of the mammary at the subclavian artery. Excellent mapping of the vascular network within the parietal pericardium was obtained and on occasion the dye could be seen in the vascular rami of the myocardium and epicardial fat. The same but more complete and detailed findings were obtained in dogs.

Eleven patients, suffering from angina pectoris caused by coronary sclerosis, were subjected to internal mammary arterial ligation by them. In each the anginal syndrome was abolished and remained so even after the patient had returned to normal activity. In addition, the signs of myocardial insufficiency particularly dyspnea disappeared in most of those in whom it was present, as did the electrocardiographic tracings of myocardial ischemia and the ballistocardiographic recordings were modified favorably in eight of the 11. In an addendum 14 additional patients obtained similar clinical and objective improvement.

This highly favorable report stimulated the authors to repeat these studies and to observe at close range the phenomena which had presented itself to the Italian workers. It must be readily admitted that considerable skepticism as to the efficacy of such findings and results was entertained. Even though anatomical channels between the internal mammary and coronary arterial systems existed, it seemed unlikely physiologically that a sufficiently increased vascular flow between the two could be obtained by such means. On the other hand if such an innocuous procedure, surgically speaking, could result in even a portion of the reported findings, then surely a contribution of considerable magnitude was at hand. Further, the realization that for its success this method might call into play and enhance naturally existing channels which the body itself employs under stress and stimulus made this investigation doubly attractive.

Anatomical Background

As early as 1880 Langer² pointed out that the vascular system of the heart was not an independent circulation. He observed the vasa propria of the heart (arterial and venous) to anastomose extensively with the vessels of the pericardium, the bronchial vessels and the diaphragm via the vasa vasorum of the great cardiac vessels. He stated that these extra-cardiac coronary anastomoses made it possible to feed the heart collaterally after the obstruction of a main coronary branch.

Gross,³ in 1921, confirmed this earlier work by showing distinct connections between the coronary arteries and the vessels of the parietal pericardium. He further commented upon the development of the rami telae adipose with advancing age with or without the stimulus of disease within the coronary arterial pathways.

In 1932, Hudson, Moritz and Wearn⁴ in a most enlightening study injected the coronary arteries at their ostia with solutions containing India ink, lamp-black or 10 per cent bismuth oxychloride under a positive pressure of 20 mm. of mercury for five minutes or longer with the heart *in situ*. The extracardiac coronary anastomoses shown in this manner were most extensive and widespread. From the major coronary vessels communications were shown to the pericardiophrenic branches of the internal mammary arteries and the anterior mediastinal, pericardial bronchial, superior and inferior phrenic, intercostal and esophageal branches of the aorta. The most extensive anastomoses between the cardiac and extracardiac vessels were around the ostia of the pulmonary veins but also along the root of the aorta, pulmonary artery, venae cavae and wherever the pericardial reflections occurred. As an extension of the same study Moritz, Hudson and Orgain⁵ reported that in four patients the extracardiac coronary anastomoses were increased due to pericardial adhesions. Beck, Tichy and Moritz⁶ employed this knowledge as a basis for the surgical production of pericardial adhesions to augment these extracardiac anastomoses.

Experimental Methods and Data

That there are significant extracardiac anastomoses with the coronary arterial bed is unquestioned. Whether these normal and slowly increasing (advancing age) intercommunications can be used as the pathway for rapidly increasing blood supply to the myocardium and promotion of intercoronary anastomoses remains to be proved. Undoubtedly such proof on a quantitative manner will be difficult if not impossible to obtain, for the very nature and diversity of the vascularity involved presents almost insurmountable problems for measurement. Great care must be taken in all experiments to avoid damage to the very vessels one is trying to evaluate.

To further verify the existence of a significant communication between the internal mammary and coronary arterial system injection studies were made in a series of normal dogs. Details of these experiments are in publication.⁷ Their results were as follows:

1. Significant quantities of dye (Evans Blue, Fluorescein and I¹³¹) injected into the internal mammary arteries at the level of the pericardiophrenic arteries were visualized in all animals in the small vessels throughout the parietal pericardium, in the mediastinal pleura and fat; around the base of the aorta and pulmonary artery and cavae; in the walls of the atria; in the epicardial fat over the atrioventricular grooves and repeatedly in the small plexus of vessels underlying the epicardium. In one in-

stance the entire thickness of the left ventricular myocardium was stained with dye even out into the base of the papillary muscles.

2. Gross dye mixed with blood was observed to flow from the distal ends of the transected circumflex or anterior descending artery in those dogs so prepared.

3. Radioactive iodine was found in the venous specimens removed from the coronary sinus in increasing amounts with the usual peak reached from five to 10 minutes after injection. The peak was somewhat variable but for the most part followed a set pattern.

4. One cm. segments of left ventricular myocardium and the posterior interventricular septum routinely contained radioactive iodine.

5. The source of this extracardiac arterial supply by the conditions of the experiment could only be by way of the pericardiophrenic artery to the parietal pericardium, thence to the myocardium under the epicardium along the roots of the great vessels and at the reflections of the pericardium.

As a natural corollary to these studies quantitative measurements of coronary backflow are desirable. As yet, these observations have not been made but preparations for such a study in this laboratory are in progress.

An attempt has been made to evaluate the degree of protection internal mammary artery ligation previously performed may afford the experimental animal when subjected to the production of sudden, acute myocardial infarction by ligation of the anterior descending coronary artery at its origin. The performance of this type of experimentation must likewise be done with great care and due regard to the variations in the anatomy of the left

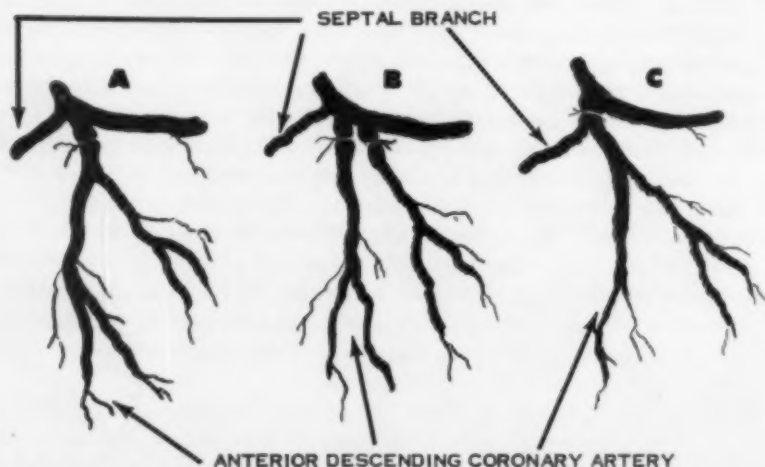


FIGURE 1: Diagram to show left coronary artery and its common variations. A is its usual pattern and point of ligation in these experiments. B—The first branch usually arising from the descending coronary shown arising from the circumflex coronary artery requiring a second ligation. C—Ligation at the origin of the descending coronary artery has inadvertently included a low lying septal branch (such ligations were excluded from this study).

coronary artery observed. The left coronary artery divides approximately 1 cm. from its origin at the aorta into the circumflex artery which continues around the heart in the atrioventricular groove and the anterior descending artery coursing down over the anterior aspect of the heart roughly overlying the interventricular septum. At this bifurcation but variably situated the septal branch arises and courses posteriorly in the interventricular septum. Just beyond the origin of the anterior descending artery its first branch which is rather large swings laterally and downward over the anterolateral aspect of the left ventricle. Thus ligation of the anterior descending artery in this experiment is designed to occlude both the anterior descending and its first branch as described but the septal branch is spared. Not infrequently the first branch of the anterior descending artery, instead of arising from its normal parent artery, arose from the first portion of the circumflex artery so that under these circumstances a separate ligature was employed to occlude it at this aberrant origin (Fig. 1). By following this method close uniformity was maintained throughout the experiment. It was hoped that survival in the control group would approximate 30 per cent so that infarct size could be compared with that of the "protected" group of animals. Dogs in the "protected" group were treated in the same manner but in these the internal mammary arteries were ligated immediately before, at 24 hours and at 48 hours before ligation of the anterior descending coronary.

In 14 control dogs the anterior descending coronary artery with the aforementioned branch to the anterolateral aspect of the left ventricle was ligated. Nine of these animals went into ventricular fibrillation and died within five to 20 minutes. Attempts to resuscitate them by defibrillation and massage were to no avail. Four others died within 24 hours. One dog lived two weeks and died in pulmonary edema. Thus, these control animals were judged on the basis of survival rather than upon size of infarction for obvious reasons.

SURVIVAL RATE IN DOGS FOLLOWING LIGATION OF
DESCENDING CORONARY ARTERY

| | Number of Dogs | Died at Operation | Died in 24 Hours | Survived 5 Days or More | Living |
|---|----------------------|-------------------------|------------------------|-------------------------------|---------|
| | 14 | 9 | 4 | 1 (7%) | 0 |
| UNPROTECTED | | | | | |
| 5 min. to 45 min. before | 4 | 0 | 1 | 3 | 2 |
| 24 hrs. before | 7 | 1 | 2 | 4 | 2 |
| 48 hrs. before | 8 | 3 | 1 | 4 | 3 |
| TOTAL | 19 | 4 | 4 | 11 (58%) | 7 (36%) |
| PROTECTED BY BILATERAL LIGATION OF INTERNAL MAMMARY ARTERIES | | | | | |

FIGURE 2: Total data obtained in 33 experiments to show a possible measure of protection provided to the myocardial circulation by bilateral internal mammary artery ligation (BIMAL).

In 19 dogs bilateral ligation of the internal mammary arteries was performed five to 45 minutes, 24 hours and 48 hours before ligation of the anterior descending coronary artery as above. The time interval seemed to make little or no difference in the degree of protection provided. Four

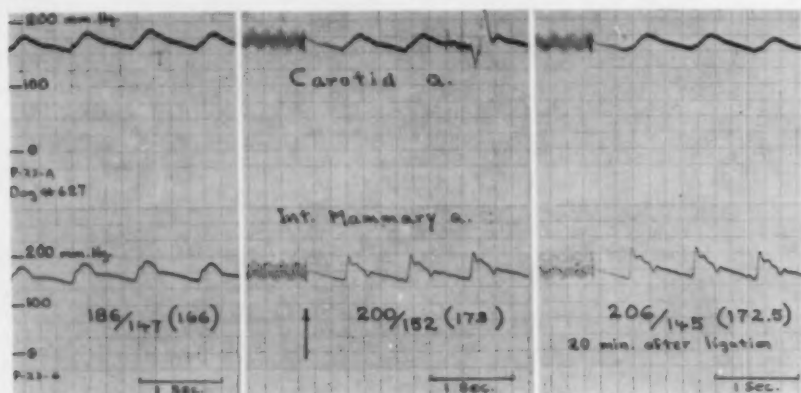


FIGURE 3: Direct pressure tracings taken within the internal mammary artery above the point of ligation at the second interspace. The arrow denotes the moment of ligation. A mean increase of 7 mm. Hg. above point of ligation is noted. The upper simultaneous tracing from the carotid artery shows the systemic pressure to remain constant.

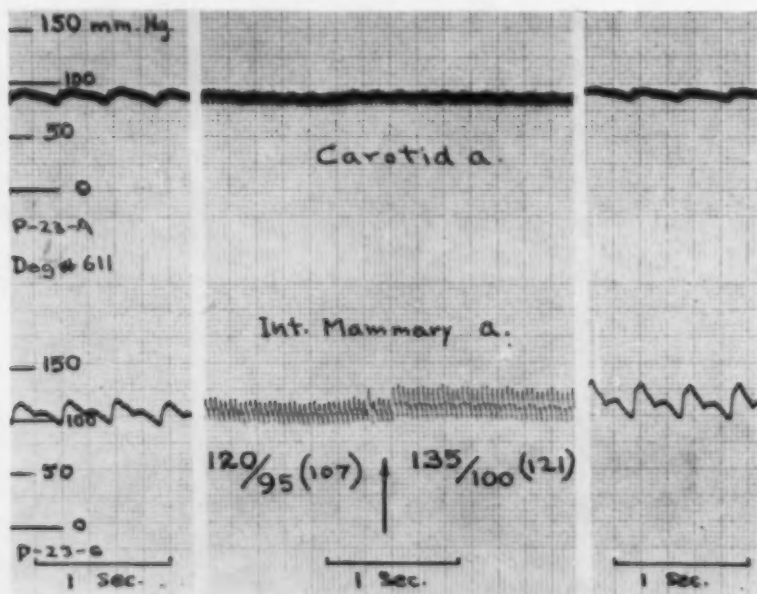


FIGURE 4: Direct pressure tracings taken within the internal mammary artery above the point of ligation at the second interspace. The arrow denoted the moment of ligation. A mean increase of 14 mm. Hg. above point of ligation is noted. Tracing on the right taken 30 minutes later.

of these animals died with a few minutes in ventricular fibrillation and four others died within 24 hours. The remaining 11 (58 per cent) dogs lived five or more days and seven (36 per cent) are still living having recovered completely (Fig. 2). Each heart of the 26 dogs who eventually died was carefully dissected and in each the septal branch from the left coronary artery was patent and uninjured. Six dogs in the original series, both among the protected and unprotected groups, were found to have had the septal branch inadvertently ligated with the anterior descending coronary artery, hence they were excluded from this analysis.

Under the conditions of this experiment which was closely controlled and meticulously performed it is felt that some degree of protection was obtained by bilateral mammary ligation in the manner described.

In an initial effort to investigate the hemodynamic pressure changes in the internal mammary artery above or proximal to the site of ligation,

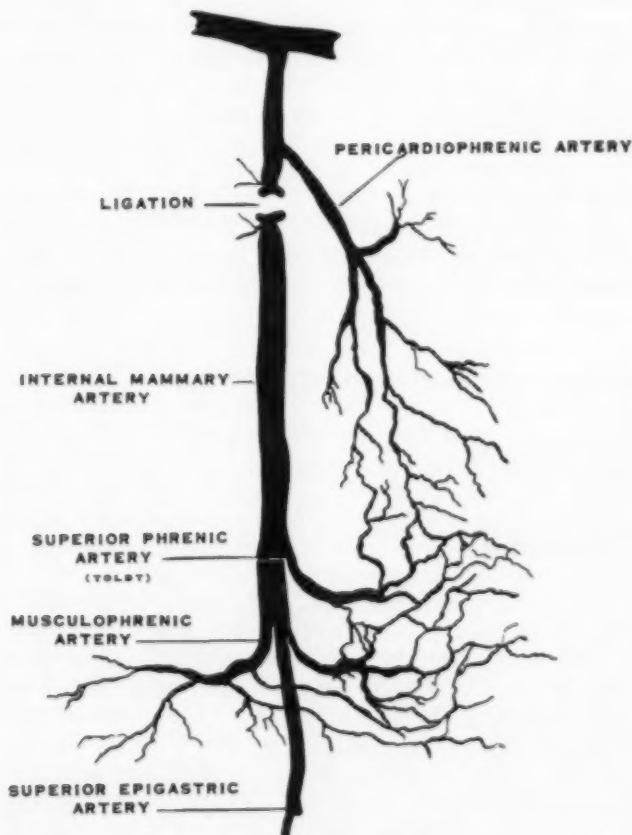


FIGURE 5: Schematic representation of internal mammary arterial collateral circulation as enhanced by ligation at the level of the second intercostal space.

pressure tracings were obtained in two animals. In one a mean pressure rise of 7 mm. Hg. (Fig. 3) was noted and in another a mean rise of 14 mm. Hg. (Fig. 4) was recorded. Each pressure rise was maintained for 20 to 30 minutes, the full period of observation. Simultaneous measurement of systemic arterial pressure in the left carotid artery showed no pressure variation.

Holman⁸ has shown that "the collateral circulation which develops following ligation of a large artery depends upon transforming high "end pressure" in the parent artery into "lateral" pressure which, directed into its branches, results in an increased volume flow through them. This increased volume flow distends them and opens up their pre-arteriolar and arteriolar beds, whence the flow is directed into the pre-arteriolar beds of the branches distal to ligation, whose low pressure because of the ligation, permits blood to flow through them more readily than through pre-arteriolar beds elsewhere." This phenomenon would seem to occur in the case of the ligated internal mammary artery where the increased pressure proximal to the ligature is transmitted down the pericardiophrenic artery into the extensive arterial plexus over the parietal pericardium. These vessels freely anastomose with those from the superior phrenic, one of the two arterial terminations of the distal internal mammary artery completing the collateral circuit (Fig. 5). It is believed, and this specific point is presently under investigation in this laboratory, that this circuit is shared by the myocardium through its extracardiac communications with the pericardiophrenic arterial system and accounts for the clinical improvement in patients so treated. It must be clearly understood, however, that this supposition has not been proved and at present is pure speculation.

Clinical Application

Even as the experimental proof for the efficacy of a procedure of this type is difficult to obtain so also is the evaluation of its clinical application. It has long been recognized that the available clinical methods for objective measurement of the status and severity of coronary artery disease, acute or chronic, are woefully inadequate. Those who have pioneered so magnificently the direct surgical approach to the problem of coronary insufficiency (Beck,⁹ O'Shaughnessy,¹¹ Fauteux,¹² Thompson,¹³ Vineberg¹⁴ and others) have repeatedly commented upon the fact that the patient's own history and subjective information is of far more importance in ultimate evaluation than are the electrocardiogram or ballistocardiogram. This has been particularly true when surgical techniques involving pericardiotomy with trauma and the introduction of foreign bodies have been employed. It may be equally true of this technique even though the pericardium and pleura are not entered or disturbed.

Because all advocated techniques to date have required open thoracotomy, erroneously considered by most physicians as highly dangerous in itself, the proper use of myocardial revascularization by these means have never attained its measurable goal. They have rarely been given a chance on a wide scale or over a long period of time. This is perhaps the fault of the

surgeon even more than of the physician because of the multiplicity of procedures advocated and their ever changing modifications. Possibly the introduction of internal mammary ligation as a means of myocardial revascularization because it is innocuous and easily tolerated even by the desperately crippled patient may break down the barrier of fear and open the way to a better understanding of what surgery has to offer. At this writing the authors are not laboring under the delusion that the operation herein reported is the *sine qua non* for coronary artery disease and should be used to the exclusion of all others. On the contrary the Beck I procedure and simple talc poudrage have demonstrated their value and are not to be abandoned or depreciated in the slightest without cause. Bilateral internal mammary artery ligation (BIMAL) to be considered on the same plane as current procedures has to prove its merit with the passage of time and time alone. It may well be that its proper place will be as an adjunct to existing measures. On the other hand should it eventuate in clinical results equal to those presently obtained by other means it will surely seek its own level and replace them. In any event it must be tested critically.

Brofman¹⁵ has stated—"The one indication for operation is a positive diagnosis of coronary disease." A more succinct and definitive statement could not be made. The patients included in this series were just that. They fall into three categories:

1. Angina pectoris due to coronary insufficiency (arteriosclerosis or hypertensive) primarily post proved infarction, occasionally without proved antecedent infarction.
2. Arteriosclerotic heart disease with coronary insufficiency resulting in myocardial insufficiency—(a) episodic heart failure, (b) arrhythmias.
3. Hemodynamic coronary insufficiency (angina) due to aortic valvular disease. True coronary artery sclerotic changes may well be absent in this group.

With the inception of any new surgical procedure invariably the clinical material referred for its application represents the last stage of the disease in question—the case in which every other therapeutic measure has failed. The patients in this series were no exception to this time honored pattern.

Ninety-two patients have been operated upon to date, the first carried out on December 5, 1956. The criteria for surgery was the presence of organic coronary insufficiency with angina pectoris as outlined above. No patient with these findings was turned down because of age, debility, unstable disease, frequency and severity of attacks, hypertension, cardiomegaly, past cardiac failure or the like as has been the case in most series reported and treated by other surgical techniques. In other words they were not carefully culled so that only the better cases were selected. The youngest was 33 and the oldest 82 years of age. Twenty-five were over 60 years, of whom eight were over 70 and two over 80. Seventy-three were men; 19 were women.

Fifty of these patients have been carefully followed for from one to five months and form the basis of this initial analysis. Evaluation of the results obtained has been the sole responsibility of one cardiologist, Dr. J. Roderick Kitchell, Chief of Cardiology at Presbyterian Hospital. Thirty-four (68 per cent) have been clinically improved in that they either have no angina (18—36 per cent) or now have fewer and less severe attacks of pain (17—32 per cent). In most of these improvement or abolition of preoperative pain and discomfort was immediate, in some 48 to 72 hours were necessary and in a few, a week or ten days elapsed before the eventual result seemed complete. In 11 (22 per cent) no clinical improvement is now apparent although several seemed improved for a time. Five have died since surgery (Table I). Six of these patients were operated upon within two weeks of an acute infarction and three of these are now dead (see below). Seven more, making a total of 13, underwent surgery within six months of an acute infarction. Much could be added to this brief recitation of figures but in a disease so protean and unpredictable more time must pass before definitive statements should be made. Representative case histories of five of these patients exemplify the type of result obtained.

TABLE I
RESULTS OF BILATERAL LIGATION AND DIVISION OF THE
INTERNAL MAMMARY ARTERIES
(50 Patients Followed 2 to 6 Months)

| IMPROVED | TOTAL GROUP | | 44 Patients Under 70 Years | |
|----------------------|-------------|----------|----------------------------|----------|
| | No. | Per Cent | No. | Per Cent |
| —Asymptomatic | 18 | 35 or 68 | 18 | 32 or 73 |
| —Moderate | 11 | | 11 | |
| —Slight | 5 | | 3 | |
| CLINICALLY UNCHANGED | | 11 or 22 | | 9 or 20 |
| Dead | | | | |
| —Within one month | 3 | 5 or 10 | | 3 or 7 |
| —Over one month | 2 | | | |

Case 1: S. C., age 64 years, had hypertension discovered in 1937. Angina pectoris was first experienced in 1947 and one year later a posterior myocardial infarction occurred. Although her weight was gradually reduced from 173 lbs. to 126 lbs., she had angina of effort and right upper quadrant pain referable to the gall bladder for the next seven years at which time cholecystectomy was performed. The angina persisted and in January 1956 left hemiparesis developed. In September 1956 she became bedfast with severe angina decubitus. She was unable to roll over or to laugh without producing severe angina. She had worn out the effect of nitroglycerin and peritrate and her pain was controlled only by the intramuscular injection of 400 to 600 mg. of demerol every 24 hours.

Physical examination revealed a well developed, elderly, white woman with a blood pressure of 140/90, pulse 84, and respirations 22. No cardiomegaly was present. There was a normal sinus rhythm and no murmurs were heard. A few moist rales in both lung bases could be heard. No masses or organs were palpable in the abdomen. There was no peripheral edema.

Routine laboratory examination revealed only a slight increase in the blood urea nitrogen to 20 mg. per cent. An electrocardiogram showed an old posterior infarction and marked anterior wall ischemia.

On January 25, 1957, she had bilateral ligation and division of the internal mammary arteries. During the next month she survived a moderately severe atypical pneumonia. Four months after operation she was still being maintained on digitalis and peritrate. Both she and her family physician recognized obvious improvement. She has been doing

household chores, has taken short walks, and now negotiates the 28 steps to her second floor apartment. The clinical improvement in this patient has been almost unbelievable.

Present electrocardiographic tracings show considerable improvement in the ischemic pattern. No ballistocardiograms were taken in this instance.

Case 2: T. J., age 54, had been well until 1947 when he suffered a posterior myocardial infarction. He had returned to work but in 1949 severe substernal pressure radiating to the left arm and through to the back with emotional upsets, on exertion and later during sleep made its appearance. When this became progressive he changed to light work. Nitroglycerin relieved his pain but resulted in severe headaches. This drug recently was losing its effectiveness.

Physical examination revealed a well developed, somewhat obese, white man with blood pressure of 180/100, pulse 78, and respirations 16. The heart was not enlarged, there was a grade I systolic murmur at the apex, and normal sinus rhythm was present. The lungs were clear to auscultation and percussion. There was no palpable abdominal mass or organ. There was slight peripheral edema but no cyanosis.

Routine laboratory examination revealed only a modest increase in the serum cholesterol to 305 mg. per cent. The electrocardiogram showed an old posterior infarction and some anterior wall ischemia. Roentgen examination failed to reveal any cardiac chamber enlargement, but there was moderate dilatation of the aorta.

The internal mammary arteries were ligated and divided on February 22, 1957. Postoperatively, he was able to return to work. Three months after the operation he suffered a mild right sided stroke. At present he is engaged in light work, still has angina with exercise and after eating for which he takes brandy and Anacin. He is considered unchanged by this operation.

Electrocardiograms and ballistocardiograms since surgery show no evidence of improvement.

Case 3: J. D., age 57, had been in apparently good health aside from slight hypertension (176/100) and marked obesity until August of 1956 when he developed chills and fever up to 105° and became comatose. He was treated for pneumonia and after partial recovery his electrocardiogram showed the presence of a posterior myocardial infarction. Shortly thereafter rather severe left precordial pain on exertion developed. This could be relieved by nitroglycerin. There was no radiation of the pain. He resumed his work and while on a trip to Europe had a severe attack of indigestion requiring a narcotic. Despite diet, peritrate, and papaverine he continued to have anginal attacks on slight exertion.

On physical examination his blood pressure was 140/92 and his pulse was 76. He was an obese man (229 pounds) in no distress at rest. There were a few rhonchi and wheezes in the left lung base. There was no detectable cardiac enlargement. There was a soft, systolic murmur at the apex. The cardiac rhythm was normal sinus. Examination of the abdomen revealed an old cholecystectomy scar, and the liver was palpable just below the costal margin.

Routine laboratory examinations were normal. The electrocardiogram showed first degree A-V block and anterior wall ischemia. Roentgen examination revealed a dilated aorta but no cardiac enlargement.

Bilateral ligation and division of the internal mammary artery was accomplished on January 29, 1957, with an uneventful convalescence. Three months later he was again running his fuel oil business and very active without pain. He was considered markedly improved.

The electrocardiogram remained unchanged. Ballistocardiograms were not taken since surgery.

Case 4: J. S., age 74, was in reasonably good health until four years prior to admission, when he began to experience exertional left precordial pain radiating to the left arm and jaw. These attacks progressed in severity and frequency and began to awaken him during the night. Two years prior to admission he suffered a cerebrovascular accident with left hemiparesis. His angina was relieved by rest and by nitroglycerin except for a more severe attack one week prior to admission which was accompanied by auricular fibrillation for which he was digitalized.

On physical examination his blood pressure ranged from 185/70 to 204/84, his pulse was 50. There was no cervical vein distension. The heart was not demonstrably enlarged and there was a grade II, systolic murmur heard at both the apex and base.

The rhythm was normal sinus. The lungs were clear to percussion and auscultation. The liver was palpable 3 cm. below the costal margin on deep inspiration as was the spleen. There was no peripheral edema.

Routine laboratory examinations were essentially normal. The electrocardiogram suggested left ventricular hypertrophy with a brachycardia of 48. Roentgen examination of the chest revealed slight left ventricular enlargement. There was no significant aortic dilatation and the lungs were normal.

Bilateral ligation and division of the internal mammary artery was accomplished on February 28, 1957. Convalescence was uneventful.

Two and one-half months later he was still having some agina both in the daytime and during sleep. He was up and about the house and able to do a little light work. He was considered to be slightly improved if at all.

The electrocardiogram remained unchanged. Ballistocardiograms were not taken in this instance.

Case 5: A. G., age 41, had polycythemia vera as early as 1945. It was treated with radioactive P³² in 1950. He also had a history of gout. He experienced coronary thrombosis in 1951 followed by suffocating, constricting type of pain in the left chest brought on by the slightest exertion, excitement, or emotional upset. More recently this same pain awakened him from sleep on numerous occasions. He gained relief from nitroglycerin and was constantly on a maintenance dose of peritrate. In November, 1955 he had a second coronary thrombosis with resultant postero-septal infarction. Following this he was maintained on dicumarol for seven months until he developed retroperitoneal hemorrhage resulting in chills, fever, and hematuria that spontaneously resolved after the drug was discontinued. His angina progressed in frequency and severity and was accompanied by dyspnea on exertion.

On physical examination his blood pressure was 112/62, pulse 66, and respirations 22. There was no cervical venous distention. The heart was not enlarged. There was no murmur. The rhythm was normal sinus. The lungs were clear to percussion and auscultation. The abdomen was soft and the liver was palpable two finger breadths below the right costal margin on deep inspiration. There was no peripheral edema.

Routine laboratory examination revealed 16 gms. of hemoglobin. The red blood cell count was 6.1 million. The white blood cell count was 10.9 thousand. Urine analysis was normal. Serum cholesterol was 264 mg. The blood urea nitrogen was 17 mg. The blood uric acid was 12.4 gm. per cent. Roentgen examination of the chest revealed only a little prominence of the left ventricle and slight aortic dilatation. The electrocardiogram showed an old postero-septal infarct and present antero-apical ischemia.

On February 21, 1957, he underwent bilateral ligation and division of the internal mammary arteries. Convalescence was uneventful. He returned to the active management of his business without pain. He plays nine holes of golf but rides a motor scooter between holes, has danced and indulges in sexual intercourse for the first time in years without angina. This patient is markedly improved.

Some electrocardiographic improvement seems to be present in that the ST segments and T wave changes have returned toward normal. A postoperative ballistocardiogram taken during the first postoperative week showed no improvement and in fact did not appear to be as good as the preoperative tracings. This is almost routinely true in ballistocardiography after any operation be it abdominal or thoracic so that one must wait for at least one month after surgery before significance can be attached to such tracings.

The underlying pathologic basis for the coronary insufficiency in this group of patients has been summarized in Table II. Although the numbers of cases are far too few to permit conclusions to be drawn the very decided impression was gained that those with hypertensive cardiovascular disease obtained the better result. Whether the hypertension favored

TABLE II
RESULTS ACCORDING TO BASIC PATHOLOGIC PATTERN

| | Arterio- sclerosis | Hypertension | Hemo- dynamic | |
|-----------------------|-----------------------|--------------------|--------------------|------------------------------|
| | | | Aortic Stenosis | Aortic Insuf- ficiency |
| TOTAL | 40 | 7 | 2 | 1 |
| —Asymptomatic | 12 | 3 | 2 | 1 |
| —Moderate improvement | 9 | 2 | 0 | 0 |
| —Slight improvement | 5 | 0 | 0 | 0 |
| | 26 (65) Per Cent | 5 (71) Per Cent | | |
| —Clinically unchanged | 9 | 2 | 0 | 0 |
| —Dead | 5 | 0 | 0 | 0 |

the development of a higher gradient of pressure within the pericardio-phrenic arterial collateral bed and therefore greater blood flow is conjectural at this point.

Of very considerable interest is the correlation of the clinical result obtained in these patients with the type and number of antecedent infarctions sustained. Such an analysis cannot be strictly accurate to the last detail for some overlapping is inevitable. The forty-five patients who have been clinically improved or unchanged suffered a total of forty-six infarctions, thus averaging approximately one infarction per patient. The five patients who died averaged more than two infarctions apiece and each of these patients suffered one septal infarction. The inference is that septal infarctions are the more hazardous and the least affected by this procedure (Table III).

Objective Findings

For some years after the introduction of true cardiac surgery there were many who could not accept the fact that patients were truly improved because of the great discrepancy between functional results and objective proof. No form of cardiac disease has shown itself to be more resistant to exact measurement than has coronary artery disease. This is not the fault of the pathologic entity but rather the inadequacy of professional instrumentation. The patient is certainly not to blame if he feels better, is more productive in society and is enjoying improved health to the consternation of the physician who just will not believe it because the improvement cannot be documented electrically. Wherein lies the answer?

Thirteen of these patients had electrocardiographic evidence of improvement and nine had improved ballistocardiograms. Curiously, only one showed improvement in both the ECG and the BCG. Thus, twenty-one patients (42 per cent) have shown objective improvement compared to 68 per cent showing clinical improvement. This comparison may not be entirely accurate for in only twenty patients have the ballistocardiograms been taken over a month from the time of surgery. Since the ballistocardiographic tracing most frequently deteriorates after any operative procedure during the first postoperative week and these patients were rou-

TABLE III
CORRELATION OF CLINICAL RESULTS WITH TYPE OF
ANTECEDENT INFARCTION

| | Anterior | | Posterior | | Septal | | Ratio of Total Infarcts |
|---------------------|----------|--------|-----------|--------|--------|--------|-------------------------------------|
| | Old | Recent | Old | Recent | Old | Recent | Number of Patients This Group |
| Improved (34 Pts.) | 9 | 3 | 13 | 0 | 11 | 1 | 37:34 |
| Unchanged (11 Pts.) | 2 | 2 | 2 | 0 | 2 | 1 | 9:11 |
| Dead (5 Pts.) | 3 | 0 | 3 | 0 | 3 | 2 | 11: 5 |

tinely discharged one week after surgery the ballistocardiographic data in over one-half of the patients (taken on the sixth postoperative day) may well be altered (Figs. 6 and 7).

Of the thirteen (26 per cent) who had improved electrocardiographic tracings after surgery the following changes were observed:

In ten the depressed ST segments returned toward normal (Figs. 6 and 7).

Nine had normal T waves.

Two had improvement in rhythm (Fig. 8).

One had a definite improvement in voltage.

In one the QRS was less slurred.

Paradoxically two patients who were unimproved clinically had improvement in their electrocardiograms and two patients who died of causes other than cardiac had brief improvement in their tracings.

Exercise tests of benefit were not employed in this series for the pre-

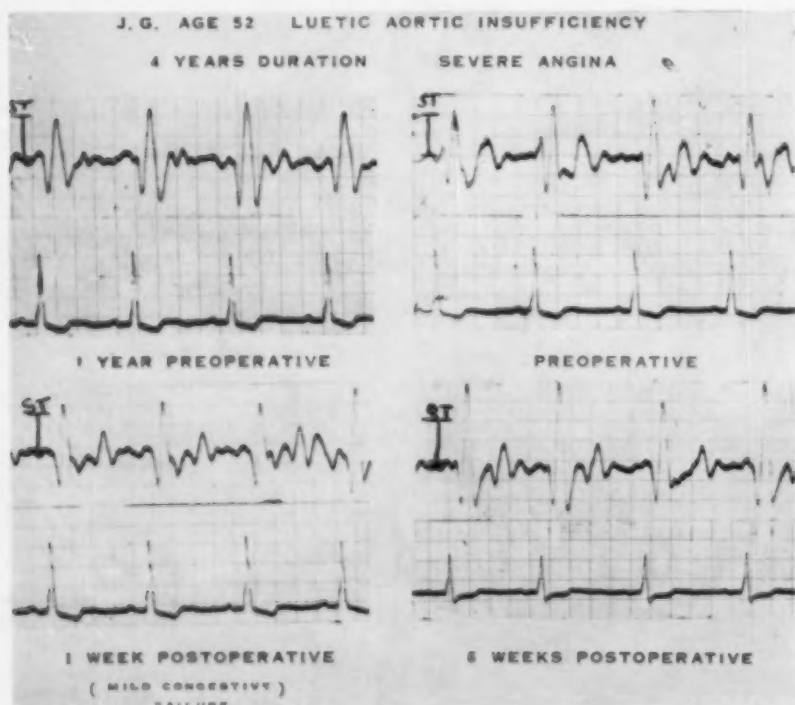


FIGURE 6: BCG and ECG tracings taken one year and two days before BIMAL (upper tracings) and one week and six weeks postoperative (lower tracing). Note the deterioration in BCG during the preoperative year, the fact that no essential improvement has occurred within the first postoperative week. In the six-week postoperative record note the considerably increased amplitude of the J waves concomitant with her marked clinical improvement.

operative diagnosis was not in question in any instance. It was felt unwise to risk the possible complication which occasionally follows such procedures in the more precarious stages of this disease.

Cause of Death

In only one of the five fatalities which occurred after surgery could there be any indictment of the surgery itself. This patient, a fifty-four year old white man, had suffered three posterior and one septal infarctions. For some hours prior to surgery anginal pain had been all but constant. The administration of Neosynephrin was necessary to obtain a blood pressure reading in the operating room. During the operation ventricular tachycardia was continuous (all cases are monitored by oscilloscopic and electrocardiographic recordings). In the recovery room his heart beat deteriorated and stopped and resuscitation was unsuccessful. The operation was obviously ill advised but there seemed to be nothing to lose and everything to gain by the attempt. An autopsy revealed several small infarctions, posterior and septal, but no large single area of necrosis. All coronary arteries showed advanced atherosclerosis. The right coronary artery was completely occluded one centimeter from its origin.

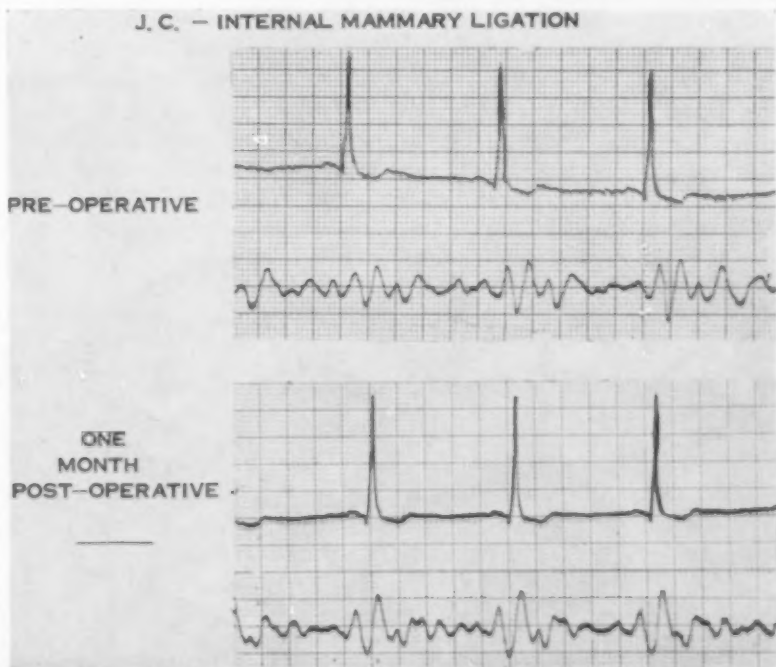


FIGURE 7: ECG and BCG tracings made preoperatively and one month postoperatively in a patient who obtained a marked improvement clinically. In the preoperative BCG record the abnormal H wave has nearly the same amplitude as the J wave. The postoperative record is practically normal with generalized improvement in amplitude.

A second patient, white, male, age fifty-three, with two healed infarctions had suffered (noted in retrospect only as all the electrocardiograms had not been available) another septal extension eighteen days preoperatively. He was allowed out of bed on the day of surgery and increased his activities on the next two days. He collapsed and died suddenly on the third postoperative day. Had the recent infarction been suspected he would have been immobilized for several weeks.

The third patient, white, male, age sixty-five, with two previous infarctions, did exceptionally well clinically and was discharged on the sixth postoperative day. An ECG taken on the day of discharge was not read until the following week. He remained pain free and active despite an unappreciated small anterior subendocardial infarct which appeared on the final ECG. He died in his sleep on the ninth postoperative day.

Two other patients, elderly white females, aged seventy-two and eighty-two respectively, and suffering from a multiplicity of diseases in addition to old anterior and septal infarctions, died thirty-five and thirty-one days after mammary ligation from pyelonephritis, adrenal insufficiency and congestive heart failure with cardiomegaly in one and generalized lymphosarcoma in the other. Both obtained marked initial relief of angina and myocardial insufficiency until the terminal stages.

Surgical Technique

The performance of bilateral division of the internal mammary arteries as compared to other surgical procedures for cardiac disease is safe, simple and innocuous in capable hands. Although the technical risk is negligible one must remember that the disease being treated is highly lethal.

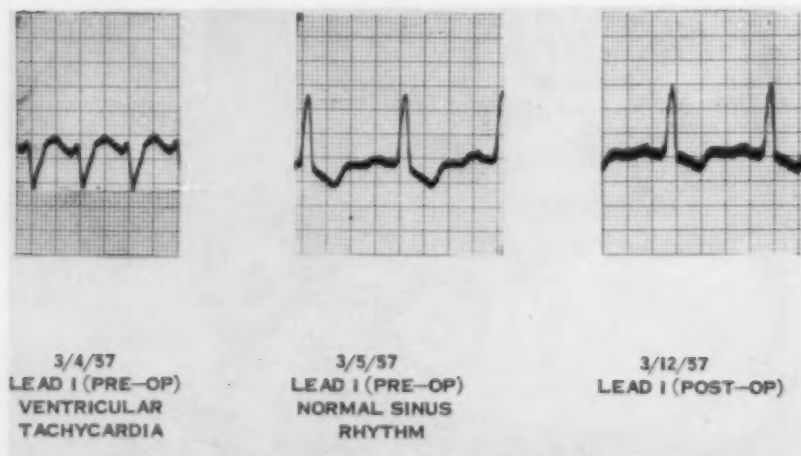


FIGURE 8: ECG tracing in a patient subject to frequent attacks of ventricular tachycardia requiring intravenous pronestyl. There has been only one mild attack postoperatively. Note the shift in axis in lead I in transition from ventricular tachycardia to the patient's usual left bundle branch block.

The application of this procedure and any other will inevitably be followed by the morbidity and mortality of severe coronary artery disease for such operations are palliative not curative.

The choice and conduct of anesthesia is of paramount importance. Two types have been used. For those whose condition is precarious and unstable a local anesthetic, 0.5 per cent procaine, is used. One side is injected and operated completely and then the other. This avoids the sudden introduction of too much anesthetic which may tend to lower the blood pressure. No more than 50 cc. of solution is necessary when used properly. Those patients who are in good condition and in whom the disease is reasonably stable easily tolerate a light general anesthesia of sodium pentothal induction and maintenance on 50 per cent N_2O and O_2 . Small amounts of succinyl choline may be used as a supplement. Endotracheal intubation is not necessary but should be available.

Bilateral hockey stick incisions are made at the lateral borders of the sternum in the second interspace. Simple transverse incisions are adequate but provide very limited exposure when the interspace is narrow and the musculature well developed. The curved incision with its reflected flap exposes the entire interspace without restriction. The pectoralis muscle is split and retracted in a normal line of cleavage. The intercostal muscles are incised midway and parallel to the ribs. The fat overlying the pleura is encountered as it surrounds the mammary vessels commonly lying one finger's breadth lateral to the sternal margin. The vein courses immediately medial to the artery and is left intact. Great care and patience must be exercised when mobilizing the artery from its areolar attachments to the pleura. The artery is divided between ligatures. The right internal mammary artery is commonly larger than the left.

The procedure may be considerably more difficult than it sounds in heavy-set, thick-muscled males. Hemorrhage and inadvertent opening of the pleura can be the only complications and usually are readily controlled. Significant changes in blood pressure must be avoided. Oscillographic and electrocardiographic monitoring is desirable but not essential.

SUMMARY AND CONCLUSIONS

1. A critical although purely preliminary attempt has been made to assess the value of bilateral ligation and division of the internal mammary arteries as a means of increasing blood supply to the myocardium. The concept for this approach is that of Fieschi. Battezzati, Tagliaferro and DeMarchi have been responsible for reintroducing and amplifying this original concept. By and large the studies reported in this discussion confirm the findings of these Italian investigators. At the moment, however, considerable reservation as to the ultimate place of this surgical procedure is warranted. Whether it will eventually remain as a surgical entity on its own merits or will be used as an adjunct to other surgical techniques cannot be decided until much more investigative work, both experimental and clinical, has been carried out.

2. That there is a naturally developing extracardiac communication between the coronary arterial and pericardiophrenic arterial vasculature has again been confirmed.

3. As yet there is no experimental proof that ligation of the internal mammary arteries bilaterally at the level of the second interspace actually increases blood flow to the heart although the supposition that it does is entertained.

4. There is the decided suggestion that in dogs ligation of the internal mammary arteries provides a measure of myocardial protection to the subsequent production of acute coronary occlusion by ligation of the anterior descending coronary artery at its origin.

5. Ligation of the internal mammary arteries at the second interspace is followed by an increase in mean arterial end pressure above the point of ligation in dogs.

6. Ninety-two patients suffering from arteriosclerotic and hypertensive cardiovascular disease with organic coronary insufficiency and angina pectoris have been subjected to bilateral mammary artery ligation (BIMAL). The angina pectoris in three of these patients was secondary to advanced aortic valve disease. Fifty of these patients have been carefully followed for one to five months. By conservative clinical evaluation 34 (68 per cent) of these patients have either lost their symptoms of pain (18—36 per cent) or have been immeasurably relieved of their discomfort (17—32 per cent). The remainder were unimproved.

7. Objective evidence of clinical improvement lags well behind the observed clinical improvement. In 13 (26 per cent) the electrocardiographic tracings taken one month or more after surgery show obvious improvement and the same may be said in nine (18 per cent) of the ballistocardiographic studies obtained. As this evidence of improvement occurred on only one occasion in the same patient, objective signs for the better have occurred in 22 (42 per cent) patients. We are indebted to and acknowledge the very considerable help rendered by Dr. Isaac Starr, Hartzell Research Professor of Therapeutics, University of Pennsylvania Medical School, who supervised and read all ballistocardiograms.

8. A simple technique for the performance of Division of the Internal Mammary Arteries has been detailed.

Addendum

A total of 150 patients suffering from organic coronary insufficiency have now been treated by bilateral ligation and division of the internal mammary arteries by the authors. Results to date in this larger series closely follow those herein reported.

RESUMEN

1. Se ha hecho intento crítico aunque netamente preliminar para estimar el valor de la ligadura bilateral de las arterias mamarias internas como un recurso para aumentar el flujo sanguíneo hacia el miocardio.

2. Las investigaciones iniciales de laboratorio confirman el desarrollo de una comunicación natural entre el sistema arterial pericardiofrénico y las raíces periféricas del sistema de la arteria coronaria.

3. En los perros, la ligadura de las mamas internas parece haber proporcionado cierta protección del miocardio cuando más tarde se hizo a ligadura de la arteria coronaria anterior ascendente. Todavía no hay prueba experimental medible de que la ligadura de las mamas internas haya resultado en aumento del flujo sanguíneo miocárdico.

4. Se han sujetado a la ligadura bilateral de las mamas (BIMAL) noventa y dos enfermos de enfermedad arterioesclerosa y cardiovascular hipertensiva con insuficiencia orgánica coronaria y angina de pecho.

En tres de estos enfermos la angina de pecho era secundaria a una enfermedad valvular avanzada de la aorta. Cincuenta de estos enfermos se han observado cuidadosamente de uno a cinco meses. Después de una valuación conservadora, 34 (68 por ciento) han perdido sus síntomas dolorosos; 18 enfermos (o sea el 36 por ciento) o bien se han aliviado de sus molestias inmensamente (17 enfermos o sea el 32 por ciento). El resto no mejoraron.

5. La evidencia objetiva de la mejoría clínica es mucho menor que la mejoría clínica observada. En 13 (25 por ciento) los trazos electrocardiográficos tomados un mes o más después de la operación muestran clara mejoría y lo mismo es de decirse en 9 (18 por ciento) de los estudios balistocardiográficos obtenidos. Como esta evidencia de mejoría ocurrió sólo una vez en el mismo enfermo, los signos objetivos de mejoría ocurrieron en 22 (42 por ciento).

RESUME

1. Une étude critique mais encore tout à fait préliminaire, a été faite pour juger de la valeur de la ligature bilatérale et de la division des artères mammaires internes, pour augmenter l'apport sanguin au myocarde.

2. Les premières investigations de laboratoire confirment qu'une communication se développe naturellement entre le système artériel péricardio-phrénique et les ramifications périphériques du système artériel coronarien.

3. Chez les chiens, la ligature des artères mammaires internes semble avoir fourni un moyen de protection myocardique lorsque la ligature de l'artère coronaire antérieure descendante était pratiquée ultérieurement. Jusqu'à présent, il n'y a aucune preuve expérimentale que la ligature des artères mammaires internes ait produit une augmentation du volume sanguin myocardique évaluable.

4. 92 malades souffrant d'affections cardio-vasculaires athéromateuses et hypertensives avec insuffisance coronarienne organique et angine de poitrine ont été soumis à la ligature bilatérale de l'artère mammaire interne. Chez trois de ces malades, l'angine de poitrine était secondaire à une affection grave de la valvule aortique. 50 de ces malades ont été suivis soigneusement pendant un à cinq mois. Des études cliniques suivies

ont montré que 34 de ces malades (68%) ou bien ont vu disparaître leurs symptômes douloureux (18 malades ou 36%) ou bien ont été incontestablement soulagés de leur gêne (17 malades, 32%). Le reste fut sans amélioration.

5. La preuve objective de l'amélioration laisse loin derrière elle l'amélioration constatée par simple observation clinique. Chez 13 malades (25%) les tracés électrocardiographiques pris un mois ou plus après l'intervention montrent une amélioration évidente et on peut en dire autant de 9 malades (18%) sur les études ballistocardiographiques qui ont été obtenues. Comme cette preuve d'amélioration n'a été constatée qu'une fois chez chaque malade, les signes objectifs d'amélioration peuvent être portés au nombre de 22 (42%).

ZUSAMMENFASSUNG

1. Es wurde ein kritischer, gleichwohl durchaus vorläufiger Versuch unternommen zwecks Bemessung des Wertes der bilateralen Ligatur und Durchtrennung der art. mam. int. als einem Verfahren zur Steigerung der Blutzufuhr des Myocards.

2. Initiale Laboratoriumsuntersuchungen bestätigen das Bestehen einer sich natürlich entwickelnden Verbindung zwischen dem Herzbeutel- und dem Zwerchfell-Arteriensystem und den peripheren Ursprüngen des Coronararteriensystems.

3. Bei Hunden scheint die Ligatur der art. mam. int. eine Massnahme zum Schutze des Myocards geschaffen zu haben, wenn anschliessend eine Ligatur der vorderen absteigenden Coronararterie vorgenommen wurde. Bisher liegt noch kein messbarer experimenteller Beweis dafür vor, dass die Ligatur der art. mam. int. eine vermehrte Durchströmung des Myocards zur Folge hat.

4. 92 Kranke, die an arterio-sklerotischen und hypertonen cardio-vasculären Krankheiten mit organischer Coronar-Insuffizienz und Angina pectoris litten, wurden einer bilateralen Ligatur der art. mam. int. unterzogen (BIMAL). Die Angina pectoris bei 3 dieser Kranken war die Folge einer beträchtlichen Erkrankung der Aortenklappen. 5 dieser Kranken wurden 1-5 Monate lang sorgfältig weiter beobachtet. Nach vorsichtiger klinischer Bewertung haben 34 (68%) dieser Kranken entweder die Schmerzerscheinungen verloren (18 Pat. oder 36%) oder wurden in nicht messbarem Grade von ihrem Unbehagen befreit (17 Pat. oder 32%). Die übrigen blieben unge bessert.

5. Die objektiven Anhaltspunkte für die klinische Besserung blieben deutlich hinter der beobachteten klinischen Besserung zurück. Bei 13 Kranken (25%) ergaben die elektrokardiographischen Aufzeichnungen, die 1 Monat oder später nach der Operation erfolgt waren, eine unverkennbare Besserung, und das gleiche kann von 9 (18%) der angestellten ballistocardiographischen Untersuchung gesagt werden. Da dieses Zeichen der Besserung nur ein einziges Mal bei dem gleichen Kranken vorkam, traten objektive Zeichen zum Besseren bei 22 Kranken auf (42%).

REFERENCES

- 1 Battezzati, M., Tagliaferro, A. and De Marchi, G.: "The Ligature of Two Internal Mammary Arteries in Disorders of Vascularization of the Myocardium," *Minerva Medica*, 46: (Part Two) 1173, 1955.
- 2 Langer, L.: "Die Foramina Thesessii im Herzen des Menschen, Sitzungsberichte Akad. Wissensch.," *Math.-naturwissensch. Cl., Wien*, 82:25, 1880.
- 3 Gross, L.: *The Blood Supply to the Heart*, New York, Hoeber, 1921.
- 4 Hudson, C., Moritz, A. and Wearn, J.: "The Extracardiac Anastomoses of the Coronary Arteries," *J. Exper. Med.*, 56:919, 1932.
- 5 Moritz, A., Hudson, C. and Orgain, E.: "Augmentation of the Extracardiac Anastomoses of the Coronary Arteries Through Pericardial Adhesions," *J. Exper. Med.*, 56:927, 1932.
- 6 Beck, C. S., Tichy, V. L. and Moritz, A. R.: "Production of Collateral Circulation to the Heart," *Proceedings of the Soc. Exper. Biol. and Med.*, 32:759, 1935.
- 7 Glover, R. P. and Davila, J. C. with Kyle, R. H., Beard, Jr., John C., Trout, R. G., and Kitchell, J. R.: "Ligation of the Internal Mammary Arteries as a Means of Increasing Blood Supply to the Myocardium," *J. Thoracic Surg.* In press.
- 8 Holman, E.: "Problems in the Dynamics of Blood Flow: 1. Conditions Controlling Collateral Circulation in the Presence of an Arteriovenous Fistula, Following the Ligation of an Artery," *Surgery*, 26:889, 1949.
- 9 Beck, C. S.: "Development of a New Blood Supply to the Heart by Operation," *Ann. Surg.*, 102:801, 1935.
- 10 Beck, C. S.: "Revascularization of the Heart," *Ann. Surg.*, 128:854, 1948.
- 11 O'Shaughnessy, L.: "Surgical Treatment of Cardiac Ischemia," *Lancet*, 1:185, 1937.
- 12 Fauteux, M.: "Pericoronary Neurectomy Associated with Ligature of Great Coronary Vein in Treatment of Some Forms of Coronary Disease," *Union Medicale du Canada*, 74:424, 1945.
- 13 Thompson, S. A. and Raisbeck, M. J.: "Cardio-cardiopexy: The Surgical Treatment of Coronary Arterial Disease by the Establishment of Adhesive Pericarditis," *Ann. Int. Med.*, 16:495, 1942.
- 14 Vineberg, A. M.: "Development of Anastomoses Between Coronary Vessels and Transplanted Internal Mammary Artery," *J.A.M.A.*, 55:117, 1946.
- 15 Brofman, B. L.: "Surgical Treatment of Coronary Artery Disease: Medical Management and Evaluation of Results," *Dis. Chest*, 31:253, 1957.

Cor Pulmonale: A Semantic Consideration, with Brief Notes on Diagnosis and Treatment

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There is a conspicuous lack of agreement as to what lesions or clinical conditions should be included in the term "cor pulmonale." Varied and conflicting views prevail throughout the literature, current and old.¹⁻¹⁸

Historically, the first use of the term cor pulmonale appears to have been in 1931 by Paul White;¹ prior to this time "emphysema heart" was in common use. In the first edition of his textbook on heart disease White speaks of "pulmonary heart disease or cor pulmonale" and indicates preference for the latter term. Twenty years later (4th edition)² he continues to speak of "cor pulmonale or pulmonary heart disease," using these terms as synonyms. In discussing the etiology of cor pulmonale he stresses "chronically increased resistance in the pulmonary circulation due commonly to narrowing of the arterioles and capillary bed," but specifically excludes from this category resistance due to "left heart failure, mitral stenosis, or congenital heart disease."

In a recent review Fishman and Richards³ define cor pulmonale as "a heart which manifests dilatation, hypertrophy, or failure secondary to intrinsic disease of the lungs;" they specifically exclude from this definition "right ventricular hypertrophy, dilatation or failure secondary to disease of the heart, e.g. mitral stenosis." On the other hand, Griffith⁴ includes right ventricular changes of mitral stenosis in the general category of cor pulmonale; he makes a distinction between "primary" cor pulmonale in which "pulmonary hypertension is the basic lesion" and "secondary" cor pulmonale "in which the basic lesion lies not in the pulmonary circuit but beyond, in the left side of the heart."

Oram⁵ broadly defines cor pulmonale as "hypertrophy and eventual failure of the right ventricle resulting from disease of the lungs, or *disorder of the pulmonary circulation*." However, when he lists the specific lesions causing disorders of the pulmonary circulation he omits all congenital cardiac lesions. Mack and Snider⁶ define cor pulmonale as "right ventricular hypertrophy resulting from disease involving the lung and pulmonary circulation" but exclude from this category "other causes of right ventricular hypertrophy, such as mitral stenosis, congenital heart disease, and left ventricular failure." Hecht,⁷ however, includes pulmonary valvular stenosis as well as "pure mitral stenosis" in which "secondary vascular changes (in the pulmonary bed) develop, apparently the result of long-standing pulmonary vascular congestion, high capillary and arte-

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⁶For a comprehensive discussion of this phase of therapy and a detailed description of specific measures the reader is referred to a recent article by Simon Dack.¹⁸

riolar pressure and precapillary and interalveolar edema." The latter author also feels that "For the sake of completeness elevation of right-sided pressure as the usual consequence of left ventricular failure should be mentioned."

Some authors^{3, 9} restrict the use of the term cor pulmonale to right ventricular lesions resulting from disease of the lung only. While it is true that intrinsic lung disease is a common cause of right ventricular strain and failure, clinical and anatomical studies indicate that the development of cor pulmonale in such cases is dependent on associated involvement of the pulmonary vascular bed. Parenchymal lung disease per se, however extensive, may leave the right ventricle completely intact if there is no coincidental interference with the flow of blood through the pulmonary circuit. Some years ago when performing postmortem examinations in a tuberculosis hospital it was impressive to observe the frequency with which a normal right ventricle is seen in the presence of extensive diffuse pulmonary parenchymal disease. Later experience in clinicopathological conferences has confirmed this earlier impression (Figure 1).

Similar observations are frequently found in the literature. Spatt and Grayzel⁸ state "The mechanism of dilatation and hypertrophy of the right

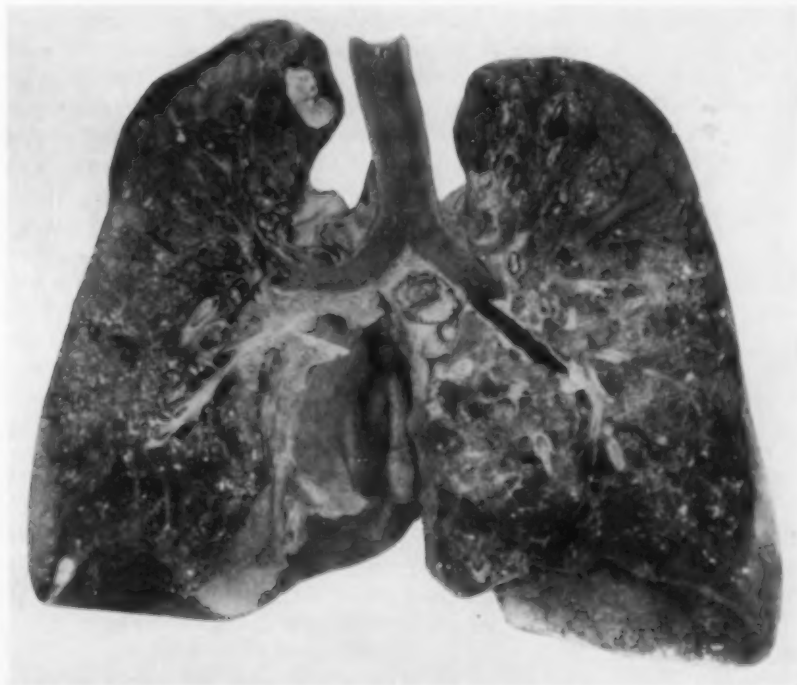


FIGURE 1: Photograph of the cut surfaces of both lungs of a patient who died of pulmonary tuberculosis; there was extreme, diffuse parenchymal disease. The heart was entirely normal. (Autopsy by Dr. Nelson Niles of the Department of Pathology of the University of Oregon Medical School.)

ventricle (in diffuse pulmonary disease) seems fairly generally agreed upon. The pulmonary changes destroy and narrow blood capillaries in the lungs, causing pulmonary hypertension, which in turn increases the strain on the right heart, thus resulting in dilatation and hypertrophy." Rubin⁹ states that in the absence of associated cardiovascular disease, a selective or preponderant enlargement of the right ventricle in emphysema is an uncommon finding. Florence McKeown¹⁰ in a postmortem study of 101 cases of emphysema found hypertrophied right ventricles in 39 and normal right ventricles in 62 cases. White and Brenner¹¹ in a study of 100 consecutive unselected autopsies found that "the majority of cases with pulmonary disease had normal right ventricles. . . . There was relative little correlation between changes in the pulmonary vascular tree and thickness of the right ventricles *except in the more marked cases*. . . . Ordinarily, asthma, emphysema and pulmonary tuberculosis, even though of high degree, do not produce cor pulmonale."

It is thus apparent that parenchymal lung disease alone does not necessarily produce strain or hypertrophy of the right ventricle. On the other hand, it is a common experience to find right ventricular hypertrophy whenever the pulmonary circulation is disturbed, even in the total absence of parenchymal lung disease. As examples of such pathological states one may cite primary pulmonary vascular sclerosis, essential pulmonary hypertension, and obstruction of the main stem of the pulmonary artery by tumor, aortic aneurysm or valvular stenosis. Hence, it would appear fair to state that in all instances where isolated right ventricular hypertrophy develops, the crucial lesion is a disturbed pulmonary circulation.

A disturbed pulmonary circulation may result from various pathological processes:

A. "Organic" Pulmonary Vascular Disease. Arteriosclerotic and/or thrombo-embolic narrowing of the pulmonary arteries and their branches (with secondary pulmonary hypertension) may be either primary as in primary pulmonary vascular sclerosis or secondary to some other pathological process. Examples of the latter are: (1) pulmonary parenchymal disease, (2) congenital cardiovascular disease, such as patent ductus arteriosus, septal defects, and other lesions with abnormal communication between the systemic and pulmonary circulation, (3) acquired cardiovascular lesions such as mitral stenosis and left ventricular failure, (4) peripheral vascular disease such as phlebothrombosis of the legs and pelvis, (5) blood dyscrasias such as polycythemia, primary or secondary, sickle-cell anemia, leukemia.

B. Hypoxia and Hypercapnia. Hypoxemia and hypercapnia due to impaired pulmonary ventilation, such as may be seen in chronic bronchitis and emphysema, may produce pulmonary hypertension with or without demonstrable morphologic changes in the pulmonary vessels. The right ventricular hypertrophy which often occurs in such cases may be due to the hypertension alone or to the combined effect of the hypertension and the hypoxemia.

C. Essential Pulmonary Hypertension. Cases of pulmonary hypertension

proved by cardiac catheterization, have been observed in which no cause for the hypertension could be demonstrated either clinically or at autopsy. It may be assumed that in such cases the hypertension and the right ventricular hypertrophy resulted from arteriolar spasm of sufficient degree to interfere with the flow of blood through the lesser circulation.

D. Hypervolemia. Strain of the right ventricle may occur even in the absence of diffuse organic pulmonary vascular disease when the volume of blood propelled through the pulmonary circuit is increased. Such a condition obtains in the presence of septal defects and other congenital lesions with abnormal communications between the lesser and systemic circulations, in pulmonary arterio-venous aneurysms, and in polycythemia, primary or secondary.

E. Mechanical Obstruction. Obstruction to the right ventricular outflow tract may result from valvular lesions—especially pulmonic stenosis, coarctation of the pulmonary artery and compression of that vessel by tumor or aortic aneurysm.

F. Chest Deformities. Kyphoscoliosis and pectus excavatum are important examples. The exact mechanism by which these lesions cause strain on the right side of the heart is not completely established. Available evidence implicates pulmonary infection and emphysema secondary to compression of portions of the lung.¹²

Right ventricular response to disordered pulmonary circulation, regardless of etiology, is constant. If a hypertrophied right ventricle were isolated from the rest of the heart, the most discerning pathologist would be unable to tell whether the cause of the hypertrophy lay in diffuse lung disease, a congenital cardiac lesion, or pulmonary hypertension due to any of the anatomical or physiological abnormalities described above.

Within this broad range, the electrocardiogram also is non-specific, revealing an "RVH" (cor pulmonale) pattern but not its cause (Figure 2). To a more limited extent this is also true of x-ray film silhouettes, especially if only posteroanterior films are available (Figure 3).

Thus three facts stand out: (1) pulmonary parenchymal disease alone, if it fails to disturb the pulmonary circulation, does not produce right ventricular hypertrophy; (2) any condition which brings about increased resistance to the flow of blood through the pulmonary vascular bed may cause right ventricular strain, hypertrophy and eventual failure; (3) the clinical and pathological manifestation of such right ventricular hypertrophy and failure follow a fixed pattern—modified only by the symptoms obviously due to the associated disease—regardless of the condition which has disturbed the pulmonary circulation.

In the light of these considerations it would seem reasonable to regard "cor pulmonale" as a generic term comprising all types of right ventricular strain and hypertrophy due to a disordered pulmonary circulation regardless of etiology. In this sense it is analogous to "cor aortale" which refers to strain and hypertrophy of the left ventricle due to a disordered systemic (aortic) circuit, as in systemic hypertension, coarctation of the aorta and aortic valvular disease. The difficulty in arriving at a concise

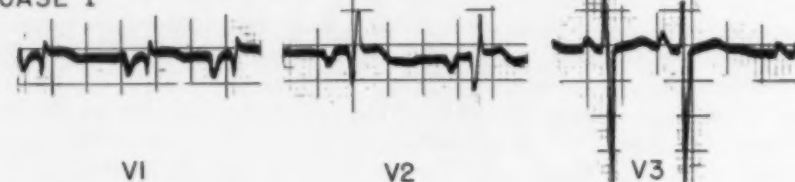
CASE 1



CASE 2



CASE 1



CASE 2

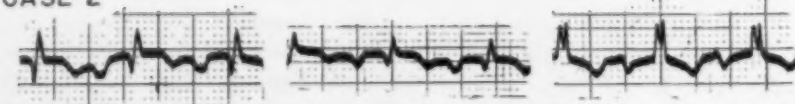


FIGURE 2: The electrocardiographic tracings on these two patients show striking similarity in the demonstration of right ventricular hypertrophy. In *Case 1*, the patient, a 56 year old woman, was found at autopsy to have intimal pulmonary arteriolar sclerosis; while in *Case 2*, a 36 year old woman, the cause for right ventricular hypertrophy was an interatrial septal defect.



FIGURE 3A

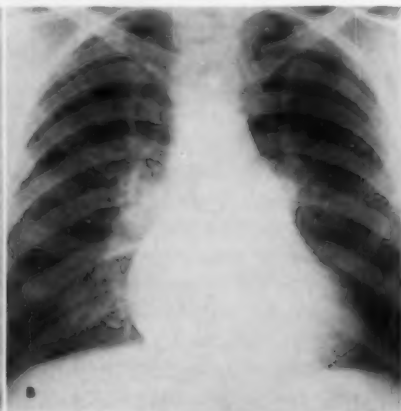


FIGURE 3B

FIGURE 3: Right ventricular hypertrophy due to: A, primary pulmonary vascular sclerosis in a 37 year old woman (autopsy), and B, mitral stenosis in a 37 year old man (surgery).

definition of cor pulmonale lies in the fact that the type of heart disease covered by that term may occur in a large variety of unrelated clinical and pathological conditions. However, when it is made clear that all these "unrelated" conditions have one thing in common, a disturbed pulmonary circulation, the difficulty disappears, and cor pulmonale may then be defined simply as right ventricular hypertrophy, strain or failure due to disordered pulmonary circulation. "Pulmonary heart disease," "emphysema heart" and "pulmonary hypertensive heart disease," often used as synonyms of cor pulmonale are less generic in their connotation. Each of these terms refers to a more or less specific etiology of the right ventricular lesion; whereas "cor pulmonale" includes all these as well as other varieties of isolated right ventricular hypertrophy due either to pulmonary or extra-pulmonary factors.

Diagnosis

This concept of cor pulmonale focuses attention upon the essential pathologic physiology. In any given case consideration of the various pathological processes which may disturb the lesser circuit points the way to a more definitive etiological diagnosis.

A history of chronic pulmonary disease is present in most instances. In cases secondary to mitral stenosis there is a background of rheumatic carditis dating from childhood. In primary pulmonary vascular disease or in primary pulmonary hypertension the history of illness is of relatively short duration—a few months to a year or two. The early manifestations are those of the underlying disease upon which are superimposed, gradually or abruptly, the symptoms of pulmonary hypertension. The latter include fatigue, dyspnea, cyanosis (often paroxysmal), dizziness, syncope and angina-like chest pains with atypical radiation. Once the symptoms become pronounced the course is rapidly downhill, terminating fatally within weeks or months. Sudden death is common.

Pertinent physical signs are dyspnea, apprehensiveness and cyanosis. Clubbing of the fingers may be present. The heart may or may not show enlargement to percussion. However, palpation will reveal a pronounced lower sternal thrust and increased systolic pulsations in the area of the conus arteriosus. A diastolic "shock" may be felt in the pulmonary area due to forcible closure of the pulmonic valves. The pulmonic second sound is greatly accentuated and systolic and diastolic murmurs along the left border of the sternum are common. Gallop rhythm may be present. In terminal stages congestive right-sided heart failure may appear; more often death occurs before gross signs of failure develop.

Radiographically, the most characteristic finding is a prominent pulmonary artery segment on the left border of the heart (Figure 3). The vascular markings in the peripheral portion of the lungs will vary with the underlying cause: they may be normal, greatly increased as in atrial septal defects and in mitral stenosis, or greatly diminished as in primary pulmonary vascular sclerosis and essential pulmonary hypertension. The heart may or may not appear enlarged; in the stage of hypertrophy without dilatation the right ventricle often looks normal on the posteroante-

rior film. With pronounced right ventricular hypertrophy and clockwise rotation of the heart, the cardiac silhouette is often enlarged to the left and may be wrongly interpreted as left ventricular hypertrophy. In point of fact this leftward extension of the cardiac shadow is due to enlargement of the right ventricle; at autopsy the left ventricle may be found even smaller than normal.

The electrocardiogram offers important aid in the diagnosis of cor pulmonale. The most definitive evidence of right ventricular hypertrophy is reversal of the QRS pattern in the precordial leads. The right precordial leads (V_1R , V_3R , V_1 , V_2) exhibit tall R-waves with relatively small S-waves and the left precordial leads (V_5 , V_6) have small R-waves and relatively deep S-waves. The onset of the intrinsicoid deflection is delayed in the right precordial leads and accelerated in the left, averaging from .03 to .05 seconds in the former and .02 to .03 seconds in the latter—likewise a reversal of the normal relationship. The T-waves are usually inverted in V_1 to V_4 and upright in V_5 and V_6 ; occasionally they are inverted in all the precordial leads, probably a reflection of associated left ventricular disease.

Less definitive patterns associated with cor pulmonale are incomplete RBBB and less frequently complete RBBB. The latter is more often seen in primary left ventricular disease but occasionally is encountered as a complication of cor pulmonale.

The standard leads usually exhibit marked right axis deviation, a non-specific sign dependent upon the vertical position and clockwise rotation of the heart (Figure 2). However, since right axis deviation is the most constant single finding in the electrocardiogram of right ventricular hypertrophy, it must be regarded as an important component of the cor pulmonale pattern.

Tall, sharply-spiked P-waves (P-pulmonale) are often seen in standard leads II and III and in AVF, probably a reflection of right auricular hypertrophy or dilatation. Although not pathognomonic, this finding affords confirmatory evidence for the diagnosis of cor pulmonale.

Two points merit special emphasis: (1) the patterns associated with cor pulmonale are independent of etiology—similar or almost identical tracings may be obtained in atrial septal defect, in primary pulmonary vascular sclerosis or in mitral stenosis; (2) a completely normal tracing may be found in well-advanced cases of cor pulmonale; hence, the absence of electrocardiographic evidence of right ventricular hypertrophy does not exclude this lesion.

Treatment

Treatment is directed primarily toward the relief of the underlying cardio-pulmonary diseases and their complications. This implies early recognition and treatment of chronic broncho-pulmonary infection (obstructive emphysema, pneumonitis, bronchitis, bronchiectasis, asthma)*, and the early surgical correction of reversible cardiac lesions and thoracic

*For a comprehensive discussion of this phase of therapy and a detailed description of specific measures the reader is referred to a recent article by Simon Dack.¹⁸

cage deformities. For essential pulmonary hypertension or primary pulmonary vascular disease (sclerotic or thrombo-embolic) little of lasting therapeutic value is available, since the underlying pathological process is essentially irreversible. Temporary favorable results have been reported from the use of ganglionic blocking agents (hexamethonium bromide)¹⁷ and from adrenolytic drugs (Priscoline).⁷ Some relief has also been reported from various surgical procedures such as sympathectomy and vagotomy. The rationale for these procedures is the assumption that a reversible increment of "spasm" is superimposed on the organic vascular obstruction.

Management of congestive failure affecting primarily the right ventricle does not differ essentially from the treatment of any other type of congestive heart failure. Digitalis, salt restriction, diuretics and regulation of activity are usually effective, albeit to a less marked degree; also the results achieved are apt to endure for a shorter period of time.

SUMMARY

Since the term *cor pulmonale* was first introduced a quarter century ago, it has come to mean different things to different people. A more rational approach to the semantology of the term is suggested. On this basis, *cor pulmonale* is defined as "right ventricular hypertrophy due to a disordered pulmonary circulation," regardless of the cause. "Pulmonary heart disease," "emphysema heart" and "pulmonary hypertensive heart disease," are types of *cor pulmonale*; each refers to right ventricular hypertrophy of more or less specific origin. Brief notes on diagnosis and treatment are presented.

RESUMEN

Desde que el término *cor pulmonale* se introdujo hace un cuarto de siglo, ha significado diferentes cosas a también diferentes personas. Una interpretación más racional del término se sugiere. Sobre esta base el *cor pulmonale* se define como "hipertrofia ventricular derecha debida a trastornos de la circulación pulmonar" cualquiera que sea la causa. "Enfermedad cardíaca pulmonar," "Corazón enfisematoso" y "Enfermedad cardíaca hipertensiva pulmonar" son formas de *cor pulmonale*. Cada uno de estos términos se refiere a hipertrofia ventricular de origen más o menos específico. Se presentan resúmenes sobre diagnóstico y tratamiento.

RESUME

Depuis que le terme de "cœur pulmonaire" a été utilisé pour la première fois il y a un quart de siècle, il est arrivé à avoir des significations différentes selon les auteurs. I. C. Brill suggère qu'on revienne à une définition proche de la signification véritable de ce terme. Sur cette base, le cœur pulmonaire doit être défini comme "une hypertrophie ventriculaire droite, due à un trouble de la circulation pulmonaire," quelle qu'en soit la cause. Le cœur des affections pulmonaires, le cœur emphysémateux, et le cœur de l'hypertension pulmonaire sont des types de cœurs pulmo-

naires; chacun d'entre eux est dû à une hypertrophie ventriculaire droite d'origine plus ou moins spécifique. L'auteur présente de brèves conclusions sur le diagnostic et le traitement.

ZUSAMMENFASSUNG

Nachdem die Bezeichnung cor pulmonale erstmals von einem Vierteljahrhundert eingeführt worden ist, ist es mittlerweile dazu gekommen, dass jedermann etwas anderes darunter versteht. Es wird eine mehr zweckmässige Einstellung auf die wirkliche Bedeutung der Bezeichnung vorgeschlagen. Auf dieser Basis wird das cor pulmonale definiert als "Hypertrophie des rechten Ventrikels infolge einer gestörten Lungencirculation" unbeschadet der Ursache. "Pulmonale Herzerkrankung," "Emphysemherz" und "pulmonale, mit Bluthahdruck einhergehende Herzerkrankung" sind Typen des cor pulmonale; jeder bezieht sich auf eine Hypertrophie des rechten Ventrikels mehr oder weniger spezifischen Ursprungs. Kurze Bemerkungen über Diagnose und Behandlung werden angeschlossen.

REFERENCES

- 1 White, P. D.: "Heart Disease," Ed. 1, New York, The Macmillan Co., 1931.
- 2 White, P. D.: "Heart Disease," Ed. 4, New York, The Macmillan Co., 1931.
- 3 Fishman, A. P. and Richards, D. W.: "The Management of Cor Pulmonale in Chronic Pulmonary Disease, With Particular Reference to the Associated Disturbances in the Pulmonary Circulation," *Am. Heart J.*, 52:149, 1956.
- 4 Griffith, G. C.: "Cor Pulmonale: Its Diagnosis and Management," *Dis. Chest*, 29: 258, 1956.
- 5 Oram, S.: "Chronic Cor Pulmonale," *The Practitioner*, 176:272, 1956.
- 6 Mack, I. and Snider, G. L.: "Respiratory Insufficiency and Chronic Cor Pulmonale," *Circulation*, 13:419, 1956.
- 7 Hecht, H. H.: "Heart Failure and Lung Disease," *Circulation*, 14:265, 1956.
- 8 Spatt, S. D. and Grayzel, D. W.: "Cor Pulmonale: Observations on Forty-Two Autopsied Patients," *Am. J. Med.*, 5:252, 1948.
- 9 Rubin, E. L.: "The Size of the Heart in Asthma and Emphysema," *Lancet*, 2:1089, 1936.
- 10 McKeown, F.: "The Pathology of Pulmonary Heart Disease," *Brit. Heart J.*, 14: 5, 1952.
- 11 White, P. D. and Brenner, O.: "Pathological and Clinical Aspects of the Pulmonary Circulation," *N. E. J. Med.*, 209:1261, 1933.
- 12 Gray, F. D., Jr.: "Kyphoscoliosis and Heart Disease," *J. Chronic Dis.*, 4:499, 1956.
- 13 Burroughs, R. W. and Sparkman, D. R.: "Diseases of the Pulmonary Circulation," *N. W. Med.*, 55:879, 1956.
- 14 Brill, I. C.: "The Clinical Manifestations of the Various Types of Right-Sided Heart Failure (Cor Pulmonale)," *Ann. Int. Med.*, 13:513, 1939.
- 15 Dexter, L., Lewis, B. M., Hayes, F. W., Gorlin, R. and Houssay, H. E. J.: "Chronic Cor Pulmonale Without Hypoxia," *Bull. New England Med. Center*, 14:69, 1952.
- 16 Barr, J. R. and Knox, Fred, H., Jr.: "Embolie Obstruction of Major Pulmonary Arteries Producing Chronic Cor Pulmonale," *Dis. Chest*, 29:225, 1956.
- 17 Davies, L. G., Goodwin, J. F. and Van Leuven, B. D.: "The Nature of Pulmonary Hypertension in Mitral Stenosis," *Brit. Heart J.*, 16:440, 1954.
- 18 Dack, S.: "The Present Status of the Treatment of Cor Pulmonale," *N. Y. State J. Med.*, 57:74, 1957.

CURRENT THERAPY

The Treatment of Shock in Myocardial Infarction

Definition of Shock of Myocardial Infarction

In evaluating the effects of treatment on the natural prognosis of "shock" accompanying myocardial infarction, it is essential to define this type of circulatory failure irrespective of the possible misuse of the term "shock" in this context. The generally accepted clinical pattern in all types of shock consists of slightly cyanotic pallor, cold skin, excessive sweating, restlessness, weakness and tachycardia. These signs vary in occurrence and intensity. The apparent critical characteristic of the life-endangering shock of myocardial infarction is severe prolonged hypotension which may occur at the onset of the attack during the first day or from the second to the fourth day.

The reported fatality rates in untreated shock of myocardial infarction range from 60 to 90 per cent. The variation arises largely from the differences in criteria of "severity" and "duration." The two elements may operate independently or concomitantly in affecting prognosis. For instance, a blood pressure that falls to an unobtainable level will represent a threat to life if it persists for 15 minutes, or even less. A fall in systolic pressure to 85 mm. Hg. which lasts for four hours, if accompanied by such evidence of circulatory inadequacy as an hourly renal output of only 10 ml. of urine, is equally likely to lead to death. The pre-infarction blood pressure apparently influences the critical level of shock production. Thus, a hypertensive patient with fixed pressures of over 180/110 mm. Hg. may enter a shocklike state when his pressure falls to 110/70 mm. Hg., whereas a person whose "normal" pressure is 94/60 mm. Hg. may exhibit no apparent shock with a fall to 80/50 mm. Hg. Fixing an arbitrary critical level of blood pressure or duration of hypotension which is applicable in all cases is impossible. Accumulated experience and reports in the literature, however, indicate that in a normotensive patient a decrease in systolic blood pressure to below 85 mm. Hg. which persists for over one hour is generally accompanied by the other features of shock and, if not treated, denotes a poor prognosis. If the hypotension persists over three hours the shock becomes "irreversible," and 90 per cent of such cases terminate fatally irrespective of possible transient response to heroic therapy.

Approximately one-half of all patients exhibiting systolic hypotension of 60 to 80 mm. Hg. for $\frac{1}{2}$ hour or less spontaneously recover without demonstrable ill effects. Hypotension with systolic blood pressure levels between 70 and 85 mm. Hg. may be maintained for 12 to 72 hours in certain patients who show no other manifestations of shock and who may excrete from 200 to 400 ml. of urine daily. However, over 80 per cent of these patients, if not treated, develop severe and fatal irreversible

shock. Attempts at correcting the hypotension are strongly recommended in such cases.

Mechanisms of Shock

The current knowledge of the basic mechanism of the shock of myocardial infarction and irreversible shock dictates to some degree the therapy employed. Two elements leading to hypotension are recognized as being precipitated by myocardial infarction. The first consists of myocardial failure and reduced cardiac output.¹⁻³ The frequent occurrence of mild to severe pulmonary edema and of prolonged circulation rates, as well as ballooning of areas of heart muscle as observed by roentgenkymography, clinically corroborates this concept. In such cases administration of oxygen by nasal cannula, mask or tent seems warranted. Digitalis glycosides are widely recommended, but whereas no contraindication exists for their use in nontoxic doses, they appear to be of little or no immediate benefit except in atrial flutter or fibrillation. The second element leading to hypotension is a peripheral vascular reaction resulting in a) failure of maintenance of arterial resistance in the presence of lowered cardiac output,⁴ and b) possible decrease of peripheral and visceral venous tone with maintenance of constriction of outlet visceral veins, resulting in venous pooling, as demonstrated experimentally in other forms of hypotension by Smith and Hoobler⁵ and by Weil, et al.⁶

Pressor Drug Therapy

The use of pressor agents, which by acting on the arterial bed and possibly on the venous bed increase arterial resistance and improve the return of blood to the heart, has been the most successful method of treating the shock of infarction. The fear that these drugs, by causing arterial constriction, may further deprive tissues of blood has not been substantiated clinically, as evidenced by the significant increase in the rate of survival of patients treated for shock with these agents. Whereas a patient with normal coronary arterial circulation may survive hypotension, those with diffuse occlusive coronary arterial disease probably require an adequate "head" of arterial pressure to avoid either additional or extended and advancing myocardial deterioration and failure.

The commonly employed pressor agents with transient action are Parendrine (hydroxyamphetamine hydrobromide), Propadrine (phenylpropanolamine hydrochloride), Neo-Synephrine (phenylephrine hydrochloride), and Wyamine (mephentermine). In addition to their vasopressor effect, the latter two drugs have an inotropic (affecting the force of muscular contractions) myocardial action. They all should be administered by intramuscular or intravenous injection in doses of 5 mg. to 25 mg., although Wyamine has been safely used in doses of 50 mg. The duration of pressor response to these drugs rarely exceeds $\frac{1}{2}$ hour. They may be repeated, but if the hypotension is severe or recurs after one to three doses, administration of long-acting pressor agents is advisable.

The most dramatic pressor effect is obtained by continuous intravenous drip infusion of *l*-norepinephrine.⁷⁻⁹ The action takes place within 30

seconds and after withdrawal ceases within a similar period. Thus, precise titration of the drug to the patient at a rate of 10 to 30 drops a minute (0.5 to 1.5 ml.) is required. The flow is maintained at a rate under 1.5 ml. per minute (2.0 to 2.5 liters per day) to avoid flooding the patient. The infusion may be introduced through a cannula placed in the inferior vena cava via the femoral vein when long periods of infusion seem probable. The drug should be given in a concentration of 4 mg. per liter of 5 per cent glucose solution; it is inactivated if given in blood or plasma. If this concentration is ineffective, the amount may be increased to 8 mg. per liter and progressively to 60 mg. per liter. On one occasion infusion of 100 mg. per liter was necessary to successfully bridge a critical period. In general, however, if infusion of *l*-norepinephrine in a concentration greater than 24 mg. per liter for over an hour is ineffective, recovery is unlikely.

During therapy the patient must be constantly monitored by skilled attendants and $\frac{1}{4}$ to $\frac{1}{2}$ hourly records of rate of flow and concentration of the drug, and blood pressure, pulse and respiration must be maintained. The cessation of the infusion is attempted only after gradual decrease of dosage, and a glucose drip is maintained for at least one hour after the drug is stopped. The reappearance of severe hypotension may quickly result in a resistant shock if the flow cannot be rapidly started.

l-norepinephrine has several undesirable effects. 1. It may cause slough of skin and deeper tissue after accidental extravasation of fluid. This may be counteracted by prompt multiple subcutaneous injections of 10 to 20 mg. of tolazoline hydrochloride (Priscoline) or of phentolamine hydrochloride (Regitine),¹¹ in 20 ml. of saline solution. 2. The transiency of the action of *l*-norepinephrine results in prompt hypotension if the infusion flow ceases abruptly. 3. The drug may lower total renal blood flow. This effect, however, has no significant influence on the favorable increase of urine secretion following restoration of adequate blood pressure. 4. The necessity of introducing 1.5 to 2.5 liters of intravenous solution may flood the patient. Flooding may be prevented by increasing the concentration of the drug in the infusion and by diminishing the rate of flow. Diuretics may be given concomitantly if fluid and sodium retention occurs, as is generally the case in shock or congestive failure and as is observed as a stress phenomenon in 75 per cent of cases of uncomplicated myocardial infarction.¹² 5. Focal hepatic necrosis has been found at autopsy in patients who received *l*-norepinephrine,¹³ but no clinical evidence of hepatic insufficiency has been noted in surviving patients treated for shock with this drug.

Griffith¹⁰ recommends adding 15 mg. of heparin to each 500 ml. of norepinephrine in 5 per cent glucose solution for intravenous drip infusion. The addition of heparin a) prevents thrombosis of the vein receiving the infusion, b) diminishes the severity of leakage sloughs, and c) possibly increases the chances of recovery from irreversible shock.

Metaraminol (Aramine)¹⁴ possesses the same advantage as norepinephrine in raising the blood pressure by inotropic effect on both heart

muscle and peripheral vascular pressor reactions. It may be administered intravenously as a drip infusion in a dose of 300 to 1000 mg. per liter of 5 per cent glucose or by intravenous injection of a single dose of 5 to 25 mg. It does not produce as rapid and as high an elevation of blood pressure as norepinephrine, and occasionally it fails to produce a pressor effect in cases where the latter drug may be successful. It has an advantage in that after the blood pressure has been raised to an effective level by drip infusion or by intravenous injection of a single dose, it may be administered subcutaneously in doses of 5 to 30 mg. at intervals of $\frac{1}{2}$ to 2- $\frac{1}{2}$ hours. This route is feasible since Aramine generally retains its pressor effect for 30 to 120 minutes and since it does not cause tissue necrosis proportionate to its pressor effect. In addition, it probably causes less decrease of renal blood flow than norepinephrine.

The mechanism of restoration of natural pressor influences is not known. With therapy the resumption of normal pressure may be either abrupt or gradual. For this reason pressor agents may be required for periods of one hour to 20 days before recovery. Six hours to three days of treatment are not unusual.

Irreversible Shock

"Irreversible" shock is likely to develop if hypotension is not corrected within three hours. Recovery occurs in only about 10 per cent of such patients treated with pressor agents. The causes of irreversible shock are not known, but several reasons have been given for the failure of a patient to respond to treatment and for the transiency of pressor responses to drugs. These are a) the release of ferritin or vasodepressor substance (VDM) by the hypoxic liver, b) the development of acidosis which diminishes the effects of pressor amine drugs, and incidentally tends toward precipitation of cardiac arrhythmias,¹⁵ c) decreased blood coagulability and formation of multiple thrombi in the lungs, brain and kidney,¹⁶ d) absorption into the blood of rapidly developing bacterial exotoxin from the hypoxic intestinal tract,¹⁷ e) further damage to the myocardium by ischemia and hypoxia as evidenced specifically by faulty carbohydrate metabolism of the muscle,¹⁸ and f) possible adrenal secretory insufficiency. In the light of these possible causes, oxygen inhalation, administration of heparin and of adequate amounts of fluid and carbohydrate by parenteral or oral routes, use of intestinal antibiotics, e.g., Bacitracin or Polymyxin, and alkalinizing therapy without concomitant sodium retention may be considered theoretically valuable. Unfortunately, none of these measures has been clinically proved to increase the chances of a patient's recovery, although all have been effective in animal experimentation. In certain cases administration of adrenal corticoids, such as hydrocortisone, 100 to 300 mg. intravenously, has seemed to potentiate the action of the pressor amine drugs, as has been demonstrated experimentally¹⁹⁻²¹; generally, however, such therapy is ineffective.

Other measures used in the treatment of shock include: 1. Rapid transfusion or plasma infusion (except in patients with elevated venous pressure) by the intravenous route (3 to 10 ml. per minute)^{22, 23} or by the

intra-arterial route (10 to 50 ml. per minute).²⁴ 2. Hypothermia has been reported by Weil in shock of bacteremic infarction²⁵ and by Vogelsang in shock of myocardial infarction.²⁶ The latter author reported that three patients with severe hypotension promptly recovered after infusion of 250 ml. of iced (4° C.) plasma. No confirmation of these results has been reported. 3. General care of the patient is important, including adequate rest without excessive use of opiates which cause respiratory depression or antidiuretic effects, attention to bowels and skin, and oral intake of food. Any serious arrhythmia should be corrected, but it should be noted that Pronestyl may accentuate the hypotension.

Conclusions

The hypotension complicating acute myocardial infarction presents a threat to life when it is manifested by a shocklike clinical pattern, especially if associated with severe oliguria. The critical level of hypotension is dependent on the pre-infarction blood pressure.

If the hypotension is very severe or persists over three hours the shock becomes irreversible and chances of successful therapy are greatly reduced. Definitive therapy should be instituted promptly and maintained until recovery is assured.

Transient benefits may be obtained by use of short-acting pressor amines and transfusions, but in general recovery is dependent on the use of the longer-acting pressor drugs, *l*-norepinephrine and metaraminol (Aramine). Constant monitoring of the patient's condition and of the therapy is necessary.

Since both myocardial failure²⁷ and peripheral vasomotor mechanisms are responsible for shock, additional measures are recommended, namely, oxygen inhalation, use of digitalis and heparin, adequate carbohydrate and fluid intake, and avoidance of sodium and water accumulation and acidosis. Adrenal corticoids may be helpful in potentiating the pressor amines, but clinically they have not proved consistently valuable.

REFERENCES

- 1 Gazes, P. C., Goldberg, L. I. and Darby, T. D.: "Heart Force Effects of Sympathomimetic Amines as a Basis for Their Use in Shock Accompanying Myocardial Infarction," *Circulation*, 8:883, 1953.
- 2 Sarnoff, S. J., Case, R. B., Berglund, E. and Sarnoff, L. C.: "Ventricular Function: V. The Circulatory Effects of Aramine; Mechanism of Action of Vasopressor Drugs in Cardiogenic Shock," *Circulation*, 10:84, 1954.
- 3 Gamill, J. F., Applegarth, J., Reed, C. E., Fernald, J. D. and Atennucci, A. J.: "Hemodynamic Changes Following Acute Myocardial Infarction Using the Dye Injection Method for Cardiac Output Determination," *Ann. Int. Med.*, 43:100, 1955.
- 4 Agress, C. M., Glassner, H. F., Binder, M. J. and Fields, J.: "Hemodynamic Measurements in Experimental Coronary Shock," *J. Appl. Physiol.*, 10:469, 1957.
- 5 Smith, J. R. and Hoobler, S. W.: "Acute and Chronic Cardiovascular Effects of Pentolinium in Hypertensive Patients," *Circulation*, 14:1061, 1956.
- 6 Weil, M. H., Hinshaw, L. B., Visscher, M. B., Spink, W. W. and MacLean, L. D.: "Hemodynamic Effects of Vasopressor Agent (Metaraminol) and Hypotension in Dogs Produced by Endotoxin," *Proc. Soc. Exper. Biol. & Med.*, 92:610, 1956.
- 7 Goldenberg, M., Apgar, V., Deterling, R. A., Jr. and Pines, K. L.: "Norepinephrine (Arterenol, Sympathin N) as Pressor Drug," *J.A.M.A.*, 140:776, 1949.

- 8 Moyer, J. H., Skelton, J. M. and Mills, L. C.: "Nor-epinephrine: Effect in Normal Subjects; Use in Treatment of Shock Unresponsive to Other Measures," *Am. J. Med.*, 15:330, 1953.
- 9 Sampson, J. J. and Zipser, A.: "Norepinephrine in Shock Following Myocardial Infarction," *Circulation*, 9:38, 1954.
- 10 Sampson, J. J. and Griffith, G. C.: "Norepinephrine in the Treatment of the Elderly Patient," *Geriatrics*, 11:60, 1956.
- 11 Close, A. S. and Kory, R. C.: "Cutaneous Necrosis Due to Norepinephrine: Mechanism and Prevention," *Clin. Res. Proc.*, 4:241, 1956.
- 12 Sampson, J. J., Kalmansohn, R. B., Klinghoffer, K. A., Friedman, M. and Toch, P.: *Sodium and Chloride Retention Following Myocardial Infarction*. Communications, 1st Congres Mondial de Cardiologie, J. B. Bailliere and Fils, Paris, 1952. Vol. 2, Pp. 448-453.
- 13 Brunson, J. G., Eckman, P. L. and Campbell, J. B.: "The Increasing Incidence of Unexplained Liver Necrosis," *U. Minn. Med. Bull.*, 28:197, 1957.
- 14 Moyer, J. H. and Beazley, H. L.: "Effectiveness of Aramine in the Treatment of Shock," *Am. Heart J.*, 50:136, 1955.
- 15 Houle, D. B., Weil, M. H., Brown, E. B., Jr. and Campbell, G. S.: "Influence of Respiratory Acidosis on ECG and Pressor Responses to Epinephrine, Norepinephrine, and Metaraminol," *Proc. Soc. Exper. Biol. & Med.*, 94:561, 1957.
- 16 Crowell, J. W. and Read, W. L.: "Hyperactivity of the Blood Coagulability Control Mechanism—A Possible Cause of Irreversible Shock," *Am. J. Med.*, 19:138, 1955.
- 17 Schweinburg, F. B., Shapiro, P. B., Frank, E. D. and Fine, J.: "Host Resistance in Hemorrhagic Shock. Demonstration of Circulating Lethal Toxin in Hemorrhagic Shock," *Proc. Soc. Exper. Biol. & Med.*, 95:646, 1957.
- 18 Hackel, D. B. and Goodale, W. T.: "Effects of Hemorrhagic Shock on the Heart and Circulation of Intact Dogs," *Circulation*, 11:628, 1955.
- 19 Kurtland, G. S. and Freedberg, A. S.: "The potentiating Effect of ACTH and of Cortisone on Pressor Response to Intravenous Infusion of L-Nor-Epinephrine," *Proc. Soc. Exper. Biol. & Med.*, 78:28, 1951.
- 20 Ramey, E. R., Goldstein, M. S. and Levine, R.: "Action of Nor-epinephrine and Adrenal Cortical Steroids on Blood Pressure and Work Performance of Adrenalectomized dogs," *Am. J. Physiol.*, 165:450, 1951.
- 21 Fritz, I. and Levine, R.: "Action of Adrenal Cortical Steroids and Nor-epinephrine on Vascular Responses of Stress in Adrenalectomized Rats," *Am. J. Physiol.*, 165:456, 1951.
- 22 Sampson, J. J. and Singer, I. M.: "Plasma and Blood Infusion Following Myocardial Infarction," *Circulation*, 9:38, 1954.
- 23 Epstein, F. H. and Relman, A. S.: "Transfusion Treatment of Shock Due to Myocardial Infarction," *New England J. Med.*, 241:889, 1949.
- 24 Berman, E. F. and Akman, L. C.: "Intra-arterial Infusion in the Treatment of Shock Resulting from Coronary Occlusion," *Am. Heart J.*, 43:264, 1952.
- 25 Weil, M. H.: "Current Concepts on Management of Shock," *Circulation*, 16:1097, 1957.
- 26 Vogelsang, A.: "Rapid Cold Plasma Infusion Treatment for Severe Shock (Peripheral Failure) Following Coronary Occlusion," *Canadian Med. J.*, 77:232, 1957.
- 27 Sampson, J. J., Felton, L. R., Goetz, A. A., Solomon, B. and Axelrad, B.: "Portable Serial Roentgenkymography in Acute Myocardial Infarction," *Circulation*, 13:729, 1956.

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THE ELECTROCARDIOGRAM OF THE MONTH

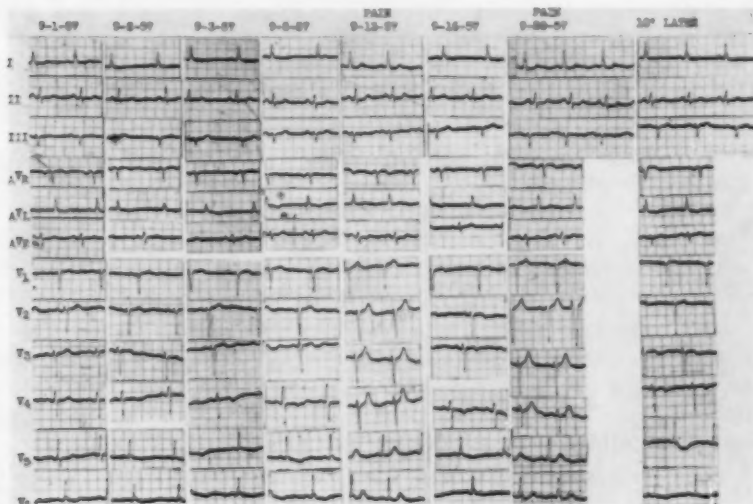
The authors would be pleased to receive comment and controversy from readers in relation to explanations offered.

A 70-year-old white woman had had intermittent discomfort in the epigastrium and lower anterior chest for several months. Attributing these to indigestion she ignored them until September 1, 1957, when a more persistent attack occurred. The electrocardiogram made on the date of admission to the hospital (September 1, 1957) and several others (September 2, 3, and 5) showed changes in the T waves. It was noted that the recurrences of discomfort that occurred in the hospital followed meals. In the mind of her physician this raised the suspicion of gall bladder disease or diaphragmatic hernia. However, it was suggested that an electrocardiogram be made *during the discomfort*. This was accomplished twice (September 13 and 20, 1957).

It is noted that previously inverted T waves became upright during each attack. As a matter of fact, the electrocardiogram of September 13 has a normal appearance except for the inverted U waves in Leads I, V₄, V₅, V₆. It is interesting to note that the U waves are upright in the same leads when discomfort is absent. Nitroglycerine invariably relieved the discomfort within three minutes.

It is important to point out that had the first electrocardiogram been made during discomfort, the one on September 13 might have been interpreted as normal (except for the inverted U waves). Accordingly, when an electrocardiographic investigation of discomfort in the chest is being carried out it is wise to record a second tracing after administering nitroglycerine. A change in the tracing following nitroglycerine such as that which occurred on September 20 is of the greatest diagnostic significance, even if no discomfort is present just prior to or during the observations.

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Editorial

The Value and Significance of International Congresses

In responding to the Editor's request for an article on the value of international medical congresses, I recall an analogy I made in discussing this subject at the Third International Congress of our College at Barcelona.

Flying up the length of the African continent with the leisurely gait of a flying boat to attend our first congress in Rome, we passed over the great African lakes, the source of the river Nile, and then over the vast Sudd region, one of the world's unique natural phenomena. For several hours, and covering hundreds of miles, we flew over a vast plain thinly covered with water so that stunted shrubs on tiny hillocks barely raised themselves above the flat mirror which continuously reflected the disc of the sun. It was this vast spongy marsh, called the Sudd, which baulked the efforts of the early geographers in tracing the Nile to its source. As we approached Khartoum we could see the river taking definite shape until, reinforced by the waters of the Blue Nile from the Abyssinian highlands, it became the mighty stream which has played so unique a part in history, as it still does in the vital economy of the land of Egypt. Carrying with it the rich silt of the African hinterland, the Nile, depositing this wealth in its lower reaches, becomes the very life-blood of Egypt; and this feature alone has made possible a civilization which has stretched back over fifty centuries.

Musing on these matters, it seemed to me to present an analogy of the manner in which we at times foregather from all quarters of the earth into a strong body with a designed scientific outlook. Meeting together thus, and pooling our knowledge, our experiences, and our discoveries, we give direction and force to the most vital of the sciences in the life of mankind. Here we crystallize ideas into vital concepts and in the fire of debate mould them into weapons against disease and death.

To many participants the stimulating atmosphere of the scientific exchanges is of the utmost value, to others again it connotes the shedding of certain shibboleths, the abandonment of methods which have been shown to be false fads. To those whose minds still retain a measure of youthful elasticity, in short, those who can accept and accommodate new ideas, such a conference can be a fine regenerating experience.

So much, very briefly, for the primary function of a great medical congress; this, at least, is the goal at which every carefully designed congress is aimed. We may not always achieve a demonstrable scientific result, but there are other effects, perhaps even more important, which are always attained in a greater or lesser degree.

The spirit of camaraderie, of brotherly helpfulness, that pervades the conference goes a long way to cement the basic friendliness of man to man, breaking down barriers of caste, of nation, and of race. United in a common bond of knowledge of the healing art, dedicated in common to the

alleviation of human suffering, we cannot fail to perceive that the service of Humanity is a thing above and apart from political and national boundaries.

The proof of this is demonstrated almost daily. Let there befall some great catastrophe, be it fire, or famine or pestilence; and we hasten to extend our help in a truly Hippocratic spirit right across political frontiers, because we are dealing with suffering fellow human-beings.

Such then is the pure humanitarian spirit which still has to find room in the hearts of our political-dictators before any conference on World Peace can be successful.

Gathered together in our great congresses, bound by the age-old dicta of Hippocrates, let us do our utmost to foster this spirit while worshipping at the altar of scientific knowledge. So doing we must inevitably spread the leavening influence of this broad humanitarianism until it breaks down the barriers and 'curtains' which still becloud our horizon.

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FIFTH INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST

Tokyo, Japan

September 7-11, 1958

Judging from advance registration and the interest expressed by physicians throughout the world, it appears that the Congress to be held in Tokyo, Japan, September 7-11, 1958, will be highly successful. The Congress is sponsored by the Council on International Affairs of the American College of Chest Physicians and presented under the patronage of the Government of Japan and the Japan Science Council, with the Honorable Nobusuke Kishi, Prime Minister of Japan, serving as the Honorary President. The Congress has been endorsed by the Japan Medical Association. The following scientific and social program will be presented.

SCIENTIFIC PROGRAM

Monday, September 8, 1958

Morning Session, Hall I—Tuberculosis

Chairmen:

Taizo Kumagai, Professor of Internal Medicine and Phthiology, Research Institute for Tuberculosis and Leprosy, Sendai, Japan
Donald R. McKay, Associate Clinical Professor of Medicine, University of Buffalo School of Medicine, Buffalo, New York, U.S.A.

Kanamycin

Hamao Umezawa, Tokyo, Japan

The Natural History of Tuberculosis in the Human Body

J. Arthur Myers, Professor of Internal Medicine and Public Health, Medical and Graduate Schools, University of Minnesota, Minneapolis, Minnesota, U.S.A.

Blood Concentrations of INH in Systemic Pulmonary Suprahepatic and Porta Venous

Ovidio Garcia-Rosell, Professor of Phthiology, University of San Marcos, Lima, Peru

In Vitro and In Vivo Activities of Kanamycin

Ken Yanagisawa, Tokyo, Japan

Tuberculin Skin Sensitivity in Old Age

O. D. Beresford, Poole Chest Clinic, Dorset, England

Diabetes and Tuberculosis: Clinical Aspects

Andrew L. Banyai, Professor of Medicine, Emeritus, Marquette University School of Medicine, Milwaukee, Wisconsin, U.S.A.

Clinical Experience in Tuberculosis

Paul Santy, Professor of Clinical Surgery, Hopital E. Herriot, Lyon, France

PANEL DISCUSSION ON TUBERCULOSIS

Moderator:

Hastings H. Walker, Medical Director, Leahi Hospital, Honolulu, Hawaii

Panel:

Miguel D. Canizares, Medical Director, Quezon Institute, Quezon City, Philippines

Imasato Donomae, Professor of Internal Medicine, Osaka University, Osaka, Japan

Peter W. Edwards, Honorary Consulting Chest Physician, Birmingham Regional Hospital Board, Market Drayton, England

Celal Ertug, Professor of Chest and Tuberculosis Service, School of Medicine, Ankara University, Ankara, Turkey

Morning Session, Hall II—Miscellaneous Topics

Chairmen:

Arao Imamura, Emeritus Professor of Medicine, Faculty of Medicine, Osaka University, Osaka, Japan

Raman Viswanathan, Director, Patel Chest Institute, University of Delhi, Delhi, India

Treatment of Hydatid Cyst of the Lung

Basile P. Karageorgis, Chief Surgeon, State Hospital, Athens, Greece

Pulmonary Eosinophilosis

John R. Wilson, Lecturer in Chest Diseases, University of Ceylon, Colombo, Ceylon

A Therapy of Tuberculosis by Intravenous, Intracavitary and Intraalveolar Instillation of Fat and Fatty Acid Colloid

Yoneji Miyagawa, Professor of Medicine, Tokyo University, Tokyo, Japan

The Use of a Reversed Gastric Tube to Replace the Esophagus

Henry J. Heimlich, Assistant Clinical Professor of Surgery, New York Medical College, New York, New York, U.S.A.

Dyspnea et Systeme Nerveux Role Diencephalique Troubles Fonctionnels

Andre Dussert, Meynard Public Sanatorium, Bergerac, France

The Significance and Possible Causes of Non-Specific Tuberculin Sensitivity

Lydia B. Edwards, Medical Director, Tuberculosis Program, Division of Special Health Services, Department of Health, Education and Welfare, Washington, D. C., U.S.A.

Experimental Anastomosis of the Pulmonary Artery to the Right Auricle

N. Salonikides, M. Frangopoulos and Constantin J. Tountas, Assistant Professor of Surgery, University of Athens Medical School, Athens, Greece

Experimental and Clinical Experience with a Valvular Prosthesis in the Correction of Interatrial and Interventricular Septal Defects

Ramon Larios, Medical Director, Sanatorio Nacional, Tegucigalpa, Honduras, Edward Fitch, Gumersindo Blanco and Charles P. Bailey, Bailey Thoracic Clinic, Philadelphia, Pennsylvania, U.S.A.

The Treatment of Pulmonary Tuberculosis from Standpoint of Surgery

Masao Tsuzuki, Medical Director, Japanese Red Cross Hospital, Tokyo, Japan

Results of Aortic Homografts Preserved in 80% Alcohol and 4% Formalin.***Experimental Study***

Giocondo Villanova Artigas, Sanatorio do Fortao-Curitiba, Curitiba, Brazil

Present Day Aspects of Cardiovascular Physiologic Problems in Aviation Medicine

H. A. Smedal, Captain, MC, United States Navy

Afternoon Session, Hall I-A - Fungus Infections**B - Clinical Aspects of Cardiopulmonary Function Studies*****Chairmen:***

Attilio Omodei Zorini, Director, Carlo Forlanini Institute, Rome, Italy

Andrew L. Banyai, Professor of Medicine, Emeritus, Marquette University School of Medicine, Milwaukee, Wisconsin, U.S.A.

Symposium on Fungus Infections***Modern Laboratory Methods in the Diagnosis of Systemic Fungus Infection, Including Tissue Cultures***

Howard Larsh, Department of Health, Education and Welfare, Public Health Service, Kansas City, Kansas, U.S.A.

Clinical Recognition and Treatment of Histoplasmosis and Blastomycosis

Michael L. Furcolow, Medical Director, Chief, Kansas City Field Station, Department of Health, Education and Welfare, Public Health Service, Kansas City, Kansas, U.S.A.

Medical and Surgical Treatment of Coccidioidomycosis

William A. Winn, Medical Director, Tulare-Kings Counties Sanatorium, Springville, California, U.S.A.

The Clinical Aspects of Cardiopulmonary Function Studies***Disability Evaluation Following Chest Injury***

Friedrich W. Koch, Städtische Krankenanstalten, Essen, Germany

Pulmonary Insufficiency Among Japanese People

Jiro Ishida, Medical Director of Tuberculosis Clinic and Hiroshi Sasamoto, Associate Professor of Medicine, Keio University, Tokyo, Japan

Principles of Ventilatory Control in Pulmonary Emphysema; Priority of Diminution of Breathing Energy over the Respiratory Center

Alvan L. Barach, Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, New York, U.S.A.

Cardiorespiratory Function in Thoracic Surgery

Miyoshi Urabe, Professor of Surgery, University of Kanazawa Medical School, Kanazawa, Japan

Comparison of Results of Pneumoangiographical Examinations with Those Obtained Through Isotope Thoracography in Lung Diseases

Wilhelm Bolt and Hans Rink, University of Cologne, Cologne, Germany

PANEL DISCUSSION ON CARDIOPULMONARY FUNCTION***Moderator:***

Noboru Kimura, Kyushu University Medical School, Fukuoka, Japan

Panel:

Alvan L. Barach, Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, New York, U.S.A.

Alfonso de la Fuente, Professor of Surgery, Faculty of Medicine, University of Madrid, Madrid, Spain

Hugo W. Knipping, Medical Director, University Clinic, University of Cologne, Cologne, Germany

Raul F. Vaccarezza, Professor of Tuberculosis, University of Buenos Aires, Buenos Aires, Argentina

Afternoon Session, Hall II—Miscellaneous Topics*Chairmen:*

Miguel D. Canizares, Director, Quezon Institute, Quezon City, Philippines
 Ovidio Garcia-Rosell, Professor of Phthisiology, University of San Marcos, Lima, Peru

Etiology and Surgical Treatment of Pigeon Chest

Henry A. Brodtkin, Chief Medical Director, New Jersey Department of Labor and Industry, Newark, New Jersey, U.S.A.

Enzyme Therapy in the Triad: Paranasal Sinus Disease, Allergic Asthmatic Bronchitis, and Bronchiectasis

Nathan E. Silbert, Chief of Allergy, Lawrence Quigley Hospital, Lynn, Massachusetts, U.S.A.

The Pharmacological Study of Tubercle Bacillus

Pyung Suh Yu, Professor of Internal Medicine, Sodo Medical College, Seoul, Korea

Post-Bronchographic Protein-Bound Iodine Levels

Somchai Bovernkitti, Sunthorn Tandhanand and Panpit Pantasuwan, Siriraj Hospital Medical School, Dhonburi, Thailand

The Cellular Structures of Tubercle Bacilli

Tadao Toda, Kenji Takeya and Massatsu Koike, Tuberculosis Institute, Kyushu University Medical School, Fukuoka, Japan

Treatment of Tuberculous Cervical Lymphadenitis

Mumtaz Hussain, Lahore, Pakistan

Effects of Isoniazid on Plasma Lipids

Lyle A. Baker, Associate Clinical Professor of Medicine, University of Illinois College of Medicine, John E. Berry and Jonas Salna, Chicago, Illinois, U.S.A.

Early Ambulation in the Treatment of Spontaneous Pneumothorax

Fred N. Miller, Director, Student Health Service, University of Oregon, Eugene, Oregon, U.S.A.

Detailed Electronmicroscopic Studies on Purified Bacterial and Viral DNA with Consideration of Their Relation to Genetics

Masanaka Terada, Professor of Bacteriology, The Tokyo Jikeikai School of Medicine, Tokyo, Japan

Treatment of Hydatid Cyst of the Lung

Yudhveer Sachdeva, Professor of Clinical Surgery, Medical College, Amritsar, India

Ten Years' Experience with Routine Chest X-Rays in a General Hospital

Walter E. Kunstler, Associate Surgeon, Royal Edward Laurentian Hospital, Montreal, P.Q., Canada

The Mitochondrial Structure of Mycobacterium Tuberculosis Relating to its Function

Toshiaki Ebina, Medical Director, Research Institute for Tuberculosis and Leprosy, Tohoku University, and Chikatomo Shinohara, Sendai, Japan

Hydatid Cysts of the Mediastinum

P. Guedj, Constantine, Algeria

Pathologisch Veränderte Lungenvenen im Hilus

Alfred Stecken, Medizinischen Klinik der Charite, Berlin, Germany

The Philadelphia Pulmonary Neoplasm Research Project

David A. Cooper, Professor of Medicine, University of Pennsylvania School of Medicine, and Katharine R. Boucot, Professor of Preventive Medicine, Woman's Medical College, Philadelphia, Pennsylvania, U.S.A.

Clinical and Roentgenological Courses of Pulmonary Paragonimiasis

Sze-Piao Yang, Professor of Internal Medicine, and Chin-Tang Huang and Lan-Chang Chiang, National Taiwan University Hospital, Taipei, Taiwan

Tuesday, September 9, 1958**Morning Session, Hall I—The Heart and Circulation***Chairmen:*

Burgess L. Gordon, Director of Education, Lovelace Foundation, Albuquerque, New Mexico, U.S.A.

Hugo W. Knipping, Medical Director, University Clinic, University of Cologne, Cologne, Germany

A Clinico-Pathological Analysis of Cardiopulmonary Death Among 300 Autopsied Cases
 Shigeo Okinaka and Hiomi Homma, University of Tokyo Medical School, Tokyo, Japan

Postthrombotic Syndrome

Mario Degni, Chief Surgeon, Casa de Saude Matarozzo, Sao Paulo, Brazil

A Preliminary Survey on Coronary Disease; Medical Research in East Pakistan

Mohammad Ibrahim, Professor of Clinical Medicine, Medical College Hospital, Dacca, Pakistan

The Diagnosis of Coronary Artery Disease

Edward C. Rosenow, Jr., Associate Clinical Professor of Medicine, University of Southern California School of Medicine, Pasadena, California, U.S.A.

Open Cardiac Surgery

Yoshio Ozawa, Professor of Medicine, Osaka University Hospital, Osaka, Japan

Principal Determinants of Coronary Flow

Lauro B. de Vera, Professorial Lecturer in Cardiac Surgery and Cardiophysiology, University of The East, Manila, Philippines, Eliot Corday, Herbert Gold, and John Williams, University of California School of Medicine, Los Angeles, California, U.S.A.

The Value of Continuous Postural Drainage in the Relief and Elimination of Chronic Cough

L. Bedford Elwell, Honorary Consultant Physician, Mater Misericordia Public Hospital, Brisbane, Australia

PANEL DISCUSSION ON CORONARY DISEASE**Moderator:**

John F. Briggs, Associate Professor of Clinical Medicine, University of Minnesota Medical School, St. Paul, Minnesota, U.S.A.

Panel:

Tachio Kobayashi, Tokyo, Japan

Hans Rink, Director, Landeskrankenhaus Marienheide, Marienheide, Germany

David H. Waterman, Thoracic Surgeon, University of Tennessee Memorial Research Center and Hospital, Knoxville, Tennessee, U.S.A.

Morning Session, Hall II—Emphysema and Miscellaneous Topics**Chairmen:**

Erik C. J. Hedvall, Professor of Phthysiology, University of Uppsala, Uppsala, Sweden

Seymour M. Farber, Associate Clinical Professor of Medicine, University of California School of Medicine, San Francisco, California, U.S.A.

Plastic Pencil Cap as a Problem of Bronchial Foreign Bodies

Jo Ono, Professor of Bronchoesophagology, Keio University Medical School, Tokyo, Japan

The Clinical Diagnosis and Classification of Mediastinal Masses

Harold A. Lyons, Associate Professor of Medicine, State University of New York Medical School, Brooklyn, Captain George L. Calvy, MC and Lieutenant Billy P. Sammons, MC, United States Navy, St. Albans, New York, U.S.A.

Physiologic Criteria for Surgery in Pulmonary Emphysema

Roger H. L. Wilson, Assistant Clinical Professor of Medicine, Orville F. Grimes and Michihiro Miyaniishi, University of California School of Medicine, San Francisco, California, U.S.A.

Lung Abscess

Kingo Shinoi, Director, Department of Surgery, Tokyo Medical College Hospital, Tokyo, Japan

Pulmonary Manifestations of Leprosy

Jean Chenebault, Chief Physician, Centre de Pneumophthisiologie Hospital Colombani, Casablanca, Morocco

Segmental Resection in Pulmonary Tuberculosis

Yoshihiko F. Fujikawa, Thoracic Surgeon, Long Beach General Hospital, Long Beach, California, U.S.A.

Maintenance of Bronchial Drainage in Emphysema

S. Thatcher Hubbard, Jr., Director, Private Cardiorespiratory Function Laboratory, Spokane, Washington, U.S.A.

Amphotericin B in the Treatment of Deep Fungus Infections Including Coccidioidomycosis, Candidiasis, Cryptococcosis, Aspergillosis and Mycetoma

Thomas H. Sternberg, Professor of Medicine, Victor D. Newcomer, Edwin T. Wright and Ronald M. Reisner, University of California Medical Center, Los Angeles, California, U.S.A.

Sarcoidosis in Puerto Rico

Hector A. Martinez-Villafane, Clinical Associate in Medicine, University of Puerto Rico, San Juan, Puerto Rico

Appearance and Behavior of the Sputum in Water. Significance of the Rate of Sinking
Prasert Kangsadal, Professor of Medicine, Siriraj Hospital Medical School, Dhonburi, Sunthorn Tandhanand and Banyat Prijyanonda, Bangkok, Thailand

The High Incidence of Peptic Ulcer in Obstructive Emphysema with Cor Pulmonale

Mack L. Gottlieb, Chief Medical Officer, United States Veterans Administration Regional Office, Manila, Philippines

The Management of Cardiospasm

David H. Waterman, Thoracic Surgeon, University of Tennessee Memorial Research Center and Hospital, Knoxville, Tennessee, U.S.A.

Staphylococcal Pneumonia; Its Treatment and Complications

William C. Rountree, Major, MC and Manard E. Pont, Captain, MC, United States Air Force

Afternoon Session, Hall I—Benign and Malignant Tumors of the Chest***Chairmen:***

Yoneji Miyagawa, Professor of Surgery, University of Tokyo College of Medicine, Tokyo, Japan

Raul F. Vaccaresza, Director, Tuberculosis Clinic and Professor of Pathology, Faculty of Medicine, University of Buenos Aires, Buenos Aires, Argentina

The Cytology of Lung Cancer in Heavy Smokers

Carlo Sirtori, Director and Professor, Istituto Nazionale per lo Studio e la Cura dei Tumori, Divisione di Anatomia e Istologia Patologica, Milan, Italy

Cancer of the Lung

Kunio Ota, Tokyo, Japan

The Incidence of Pulmonary Neoplasms in the World

Giovanni L'Eltore, Assistant Director, Carlo Forlanini Institute, Rome, Italy

Considerations of a Pathologist about the Cytodiagnosis of Bronchial Tumors, 500 Cases

Bernard Pierson, Chief of Research, Pathologic Anatomy, University of Nancy, Nancy, France

Cancer of the Lung

Kingo Shinoi, Professor of Medicine, Tokyo Medical College, and Shichiro Ishikawa, Assistant Professor of Medicine, Keio University Medical School Hospital, Tokyo, Japan

Pulmonary Cytology in Malignant and Nonmalignant Chest Diseases

Seymour M. Farber, In Charge, University of California Tuberculosis and Chest Service, San Francisco Hospital, Samuel L. Pharr and Ikuma Nagasawa, San Francisco, California, U.S.A.

The Importance of Pleural Biopsy for Research, Diagnosis and Therapy

Anton Sattler, Professor of Medicine, University of Vienna, Vienna, Austria

PANEL DISCUSSION ON BENIGN AND MALIGNANT TUMORS OF THE CHEST***Moderator:***

Donato G. Alarcon, Professor of Clinical Medicine, National University of Mexico, Mexico City, Mexico

Panel:

Jean M. Dubois de Montreynaud, Pneumologist, Centre Régional Anti-Cancereux, Reims, France

Chevalier L. Jackson, Professor of Laryngology and Bronchoesophagology, Temple University Medical Center, Philadelphia, Pennsylvania

Helge B. Wulff, Professor of Surgery, Lund University, Malmö, Sweden

Hisao Yamashita, Tokyo, Japan

Afternoon Session, Hall II—Cardiopulmonary Disease and Pediatrics***Chairmen:***

M. R. Heynsius van den Berg, President, Royal Netherland-Central Association for the Prevention of Tuberculosis, Amsterdam, The Netherlands

Giovanni L'Eltore, Assistant Director, Carlo Forlanini Institute, Rome, Italy

Critical Conditions for Pneumonectomy and Their Management

Shichiro Ishikawa, Assistant Professor of Medicine, Keio University Medical School Hospital, Tokyo, Japan

Surgical Correction of Transposition of the Great Vessels

Thomas G. Baffes, Department of Surgery, Northwestern University Medical School, Chicago, Illinois, U.S.A.

The Diagnosis and Treatment of Arteriovenous Coronary Aneurysms in Infants and Children

Benjamin M. Gasul, Director, Pediatric Cardiophysiology Department, Cook County Children's Hospital, Chicago, Illinois, U.S.A.

Thirty-Three Year Review of Rheumatic Fever and Rheumatic Heart Disease in Rhode Island (1925-1958)

Banice Feinberg, Physician in Chief, Department of Pediatrics, Rhode Island Hospital, Providence, Rhode Island, U.S.A.

Cardiovalvulosectomy

Shigeru Sakakibara, Professor of Surgery, Heart Institute, Woman's Medical College, Tokyo, Japan

Lung Ventilation in Mitral Stenosis

Nicholas Tsamboulas, Professor of Medicine, E. Economides and G. Hadji Dimitriou, University of Athens, Athens, Greece

Isoniazid Therapy of Primary Tuberculosis in Children

Katherine H. K. Hsu, Assistant Professor of Pediatrics, Baylor University School of Medicine, Houston, Texas, U.S.A.

Therapeutic Pneumoperitoneum in Tuberculous Filipino Children

Mita Pardo de Tavera, Resident Physician, and Gloria Calderon, Quezon Institute, Quezon City, Philippines

Results from Current Trials of the Prophylactic Possibilities of Isoniazid in Preventing Meningitis and Other Complications of Primary Tuberculosis in Children

Frank Mount, Operational Research Section, Public Health Service Tuberculosis Program, Washington, D.C., U.S.A.

Immunization Against Tuberculosis with a Synthetic Antigen

Alberto P. Leon, Professor of Infectious Diseases, National University School of Medicine, Mexico City, Mexico

Myxosdema Heart in Children

I. P. Bronstein, Professor of Pediatrics, University of Illinois College of Medicine, Chicago, Illinois, U.S.A.

Wednesday, September 10, 1958**Morning Session, Hall I—Cardiovascular and Pulmonary Surgery****Chairmen:**

Peter W. Edwards, Honorary Consulting Physician, Birmingham Regional Hospital Board, Market Drayton, England

J. E. J. Harris, Director, Student Health, University of New Mexico, Albuquerque, New Mexico, U.S.A.

Open Cardiac Surgery

Seiji Kimoto, Professor of Surgery, Tokyo University Hospital, and Shigeru Sakakibara, Tokyo, Japan

Funnel Plastic: A Treatment for Chronic Empyema Cavity

Karl Vosschulte, Professor of Surgery, University of Giessen, Giessen, Germany

Intracardiac Surgery Under Hypothermia and Extracorporeal Circulation

Helge B. Wulff, Professor of Surgery, Lund University, Malmö, Sweden

Demography of Cancer of the Lung

Donato G. Alarcon, Professor of Clinical Medicine, National University of Mexico, Mexico City, Mexico

Gross-Pleuropneumectomy

Nunzio M. DiPaola, Professor of Surgery, University of Rome, Rome, Italy

PANEL DISCUSSION ON AVIATION MEDICINE**Moderator:**

Burgess L. Gordon, Director of Education, Lovelace Foundation, Albuquerque, New Mexico, U.S.A.

Panel:

James M. Davis, Lt. Col., MC, Director, Professional Services, Pacific Air Forces, United States Air Force

M. Frederick Leeds, Pan American World Airways, San Francisco, California, U.S.A.

Masamitsu Oshima, Tokyo, Japan

A. S. R. Peffers, Senior Medical Officer, British Overseas Airways Corporation, London, England

H. A. Smedal, Captain, MC, United States Navy

Morning Session, Hall II—Occupational Diseases of the Chest**Chairmen:**

Paul Santy, Professor of Clinical Surgery, Hopital E. Herriot, Lyon, France

Anton Sattler, Professor of Medicine, University of Vienna, Vienna, Austria

Silicosis

Takashi Nakamura, Professor of Medicine, Tohoku University, Sendai, Japan

Certain Etiologic, Pathogenic and Clinical Aspects of Pneumoconiosis

Raul F. Vaccarezza, Professor of Phthisiology, University of Buenos Aires, Buenos Aires, Argentina

Manganese Intoxication

Ubaldo Roldan V., Professor of Medicine, National University of Mexico, Mexico City, Mexico

Studies on Asbestosis

Zenji Horai, Professor of Medicine, Nara Medical College, Osaka, Japan

Silicosis

C. J. B. Muller, Head, Department of Radiology, Karl Bremer Hospital and University of Stellenbosch Medical Faculty, Cape Town, South Africa

Follow Up Studies of Simple Silicosis Among Retired Miners

Shuei Nozaki, Niigata, Japan

A Review of Berylliosis Therapy

Harry E. Tebrock, Assistant Professor of Research Pharmacology, University of Miami School of Medicine, Douglaston, New York, U.S.A.

Serum Isoniazid Concentrations in Japanese Females and the Effect of the Simultaneous Administration of PAS

W. C. Morse, Major, MC, T. S. Rei, F. T. Roque, Lt. Col., MC., and C. S. Christianson, Lt. Col., MC, United States Army, Camp Zama, Japan

Rheumatoid Pneumoconiosis

Jethro Gough, Professor of Pathology, Welsh National School of Medicine, Cardiff, Wales

Koniomycoses from Occupational Vegetable Powder Inhalation

Balazs Bugyi, Budapest, Hungary

Surgical Management of Acute Respiratory Emergencies

Henry J. Stanford, Thoracic Surgeon, Tucson Medical Center, Tucson, Arizona

Afternoon Session, Hall I—Bronchoesophagology and Miscellaneous Topics**Chairmen:**

Donato G. Alarcon, Professor of Clinical Medicine, National University of Mexico, Mexico City, Mexico

Jo Ono, Professor of Bronchoesophagology, Keio University Medical School, Tokyo, Japan

The Historical Review of Chest Surgery in Japan

Hiroshige Shiota, President, Nippon Medical College, Tokyo, Japan

Vascular Anomalies Obstructing the Trachea and Esophagus; Their Diagnosis and Treatment

Paul H. Holinger, Professor of Bronchoesophagology, University of Illinois College of Medicine, Kenneth C. Johnston, William E. Riker and Willis J. Potts, Chicago, Illinois, U.S.A.

An Analysis of Five Year Survival Cases Following Radical Esophagectomy for Esophageal Cancer

Komei Nakayama, Professor of Surgery, Chiba University School of Medicine, Chiba City, Japan

Reconstruction of the Esophagus

Kwang-Shun Lu, Professor of Thoracic Surgery, National Defense Medical Center, Taipei, Taiwan

The Endoscopic Therapy of Parenchymal Tuberculosis

Albert A. Carabelli, Chief of Thoracic Medicine, St. Francis Hospital, Trenton, New Jersey, U.S.A.

Surgical Indications in Cancer of the Lung

Ettore Ruggieri, Director of Surgical Clinic, University of Naples, Naples, Italy

Cancer of the Esophagus

Luji Katsura, Sendai, Japan

Fifteen Unrecognized or Neglected Physical Signs in the Diagnosis of Chest Diseases

Coleman B. Rabin, Assistant Clinical Professor of Medicine, Columbia University, New York, New York, U.S.A.

The Study of Mycosis on a National Wide Scale Program Developed in Venezuela by the National Coordinating Commission

Jose Ignacio Baldo, Professor of Phthisiology, Central University School of Medicine, Caracas, Venezuela

The Pathology and Pathogenesis of Histoplasmosis

Henry C. Sweany, Director of Research, Pathology and Allied Sciences, Missouri State Sanatorium, Mount Vernon, Missouri, U.S.A.

A New Method of Treatment of Emphysema by Tracheal Fenestration

Edgar Mayer, Clinical Professor of Medicine, New York University Post Graduate Medical Center, Israel Rappaport and E. E. Rockey, New York, New York

Afternoon Session, Hall II—Miscellaneous Topics*Chairmen:*

Eung Soo Han, Assistant Professor of Internal Medicine and Bacteriology, Taegu Medical College, Seoul, Korea

Hastings H. Walker, Medical Director, Leahi Hospital, Honolulu, Hawaii

The Relationship Between the Structure of the Pulmonary Lymph System and the Genesis and Development of Pulmonary Diseases

Chuzo Nagaishi, Professor of Surgery, Kyoto University, Kyoto, Japan

Ten Year Follow-Up of Antimicrobial Treatment of Pulmonary Tuberculosis

Hyman I. Sapoznik, Attending Physician, Chest Department, Michael Reese Hospital and David B. Radner, Chicago, Illinois, U.S.A.

Spontaneous Pneumothorax in Hawaii

Edmund L. Lee, Queen's Hospital, Honolulu, Hawaii

The Pathogenesis of Tuberculosis and the Prevention of Cavity Formation

Yuichi Yamamura, Professor of Biochemistry, Kyushu University Medical School, Toyonaka, Japan

Spontaneous Pneumothorax

Ralph Volk, Captain, MC, United States Navy, Yokosuka, Japan

Antituberculosis Program for El Salvador

Jose F. Valiente, Professor of Tisiology, University of El Salvador Medical School, San Salvador, El Salvador

Congenital Bronchoesophageal Fistula Without Esophageal Atresia

Bomy R. Billimoria, Honorary Thoracic Surgeon, St. George's and Masina Hospitals, Bombay, India

The Role of Humoral Factors in Native and Acquired Resistance to Tuberculosis

Shuusuke Tsuji, Professor of Medicine, Kyoto University, Kyoto, Japan

The Results of the Ambulant Chemo-Antibiotic Therapy from the Central Dispensary in Stockholm

Isador L. Bluhm, Docent Professor, Karoline Institute, Stockholm, Sweden

Laryngo-Tracheal-Bronchial Local Anesthesia by Nebulization

Aldo G. Remorino, Bronchoscopist, Hospital de los Ninos, Buenos Aires, Argentina

Die Contusio Thoracis und ihre Folgen

Helmut P. Kuemmerle, Universitäts-Frauen-Klinik, Tuebingen, Germany

Surgical Treatment of Tuberculous Branchostenosis and Hilar Lymphatic Tuberculosis

Yujiro Dotai, Keio University College of Medicine, Kanagawa, Japan

Present Status of Tuberculosis in Ceylon

George E. Ranawake, Chief of Tuberculosis, Ceylon Medical Department, Colombo, Ceylon

Pulmonary Manifestations of Some Tropical Diseases in Thailand

Ninat Chinachoti, Central Chest Clinic, and Banyat Priyjanonda, Bangkok, Thailand

The Problem of Non-Specific Stimuli in the Treatment of Pulmonary Tuberculosis

Lucjan A. Dobrowolski, Pulmonary Disease Hospital, Warsaw, Poland

Historical and Modern Advances in Cardiac Surgery

Elmer C. Rigby, Chief Consultant, Thoracic Surgery, State of California, Los Angeles, California, U.S.A.

Thursday, September 11, 1958**Morning Session, Hall I—Tuberculosis***Chairmen:*

Jose Ignacio Baldo, Professor of Phthisiology, Central University of Venezuela, Caracas, Venezuela

Manuel Quisumbing, San Pablo City Hospital, San Pablo, Philippines

Control of Tuberculosis in Iran

Mohamad Yazdi, Director, Sanatorium Niavaran, Tehran, Iran

Cicatrical and Open Healing of Tuberculous Pulmonary Cavities and its Impediments

Taizo Kumagai, Tohoku University, Sendai, Japan

Present Developments of Isoniazid Chemotherapy Against Tuberculosis in the Fields of Experimental, Human and Bovine Disease Protection

Attilio Omodei Zorini, Director, Carlo Forlanini Institute, Rome, Italy

Resection and Thoracoplasty

Paul Kyrle, Department of Surgery, University of Vienna, Vienna, Austria

A Strain Directly Producing Dihydrostreptomycin

Mitsuo Hori and Arao Imamura, Osaka University, Osaka, Japan

Treatment of Pulmonary Tuberculosis with Thiosemicarbazone-Isonicotil Hydrazide

Miguel Jimenez Sanchez, Professor of Clinical Medicine, Anti-Tuberculosis Sanatorium, Huipulco, Mexico

Scalene Node Biopsy (Daniels' Operation) in the Diagnosis of Diseases of the Chest

Erik J. Hedvall, Professor of Phthisiology, Uppsala University, Uppsala, Sweden

Tuberculosis in Industry

P. K. Ghosh, Associate Professor of Medicine, R. G. Kar Medical College Hospitals, Calcutta, India

Atypical Acid Fast Bacilli and Their Clinical Significance

Emil Bogen, Pathologist, and Ann D. Staatz, Head Physician, Olive View Sanatorium, Olive View, California, U.S.A.

The Value of Chemotherapy for Active Pulmonary Tuberculosis Patients Treated on an Out-Patient Basis in Korea

Eung Soo Han, Assistant Professor of Internal Medicine and Bacteriology, Taegu Medical College of Korea, Kiho Kim and Hae Won Pyun, Seoul, Korea

Morning Session, Hall II—Miscellaneous Topics***Chairmen:***

Pholpoke Thip, Instructor in Surgery, Army Medical Service School, Bangkok, Thailand

M. Jay Flipse, Jackson Memorial Hospital, Miami, Florida, U.S.A.

Tumors of the Thymus Gland

Seizo Katsunuma, President, Nagoya University, Nagoya, Japan

Differential Diagnosis and Therapy of the Pulmonary Manifestations of Collagen Diseases

Dieter Koch-Weser, Associate Professor of Medicine, Western Reserve University School of Medicine, and Antonio Carlos Debes, Cleveland, Ohio, U.S.A.

Pulmonary Acariasis

Manabu Sasa, Tokyo, Japan

The Detection of M. Tuberculosis in Sputum by the Use of X-Irradiated Guinea Pigs

Joseph A. Schwartz, Assistant Professor of Medicine, University of California Medical School, Charles M. Carpenter and A. W. C. Naylor-Foote, Los Angeles, California, U.S.A.

Pulmonary Paragonimiasis in Japan

Ichiro Miyazaki, Fukuoka, Japan

Gastrointestinal Manifestations in Posterior Wall Myocardial Infarction

A. David Etes, Attending Physician, Loomis Hospital, Liberty, New York

Surgical Casectomy

Yasuyuki Kano, Professor of Surgery, Keio University, Tokyo, Japan

Vocal Cord Paralysis Related to Diseases of the Neck and Thorax

Nathaniel M. Levin, Clinical Assistant Professor of Surgery, University of Miami School of Medicine, Miami, Florida, U.S.A.

Bronchiectasis and Cystic Diseases of the Lung

Naoshi Kumagai and Shogo Awataguchi, Tohoku University, Sendai, Japan

Radiological Evaluation of the Heart Size in Relation to Surface Area and Shape of Chest in Normal Individuals

Samuel A. Weisman, Clinical Associate Professor of Medicine, University of Southern California, Norman Zheutlin and Bernard J. O'Loughlin, University of California, Los Angeles, California, U.S.A.

Steroid Therapy and Tuberculosis

Harry Shubin, President of Staff and Chief, Department of Pulmonary Diseases, Philadelphia General Hospital, Philadelphia, Pennsylvania, U.S.A.

Roentgenologic Problems in Chest Diseases

Hans Martin Landecker, Honorary Chest Physician, Chest Clinic, Anti-tuberculosis Association, Sydney, Australia

A Simple Method for Evaluating a New Oral Bronchodilator

Richard I. H. Wang, Indianapolis General Hospital and Robert E. Shipley, Indianapolis, Indiana, U.S.A.

Pulmonary Bilharziasis

Taha M. Gomaa, Assistant Professor of Medicine, Cairo University, Cairo, Egypt

The Treatment of Various Forms of Primary Infections with Cortico-Steroids

Joaquin Escobar Perez, Assistant Professor of Medical Pathology, San Carlos University, Guatemala City, Guatemala

Coincident Pulmonary Tuberculosis and Respiratory Symptoms from Extrinsic Allergy

Ruth W. Wilson, Clinic Chief, State Tuberculosis Clinic, Rochester, Pennsylvania

The Problem of Tuberculosis in East Pakistan

Mohammed Giasuddin, Dacca, East Pakistan

FIRESIDE CONFERENCES**Subjects and Discussion Leaders****Thursday afternoon, September 11****Management of Emphysema**

Andrew L. Banyai, Professor of Medicine, Emeritus, Marquette University School of Medicine, Milwaukee, Wisconsin, U.S.A.

Alvan L. Barach, Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, New York, U.S.A.

Donald R. McKay, Associate Clinical Professor of Medicine, University of Buffalo School of Medicine, Buffalo, New York, U.S.A.

Makoto Murao, Chief, Internal Medicine, Tokyo University Hospital Policlinic, Tokyo, Japan

Tetsuro Yokoyama, Assistant, Department of Medicine, Cardiopulmonary Laboratory, Keio University, Tokyo, Japan

Cardiac Physiology: Vectorcardiography: Ballistocardiography

Eiichi Kimura, Sendai, Japan

Noboru Kimura, Kyushu University Medical School, Fukuoka, Japan

E. A. McMaster, Internist, Seaforth Medical Clinic, Seaforth, Ontario, Canada

Yasushi Mizuno, Nagoya University Hospital, Nagoya, Japan

Shiro Osajima, Professor of Internal Medicine, Nagasaki, Japan

Gerhard Schumacher, Chief of Internal Medicine, Rittberg Hospital, Berlin, Germany

Treatment of Pulmonary Infections, Medical and Surgical

Seymour M. Farber, Associate Clinical Professor of Medicine, University of California School of Medicine, San Francisco, California, U.S.A.

Sukehiro Higuchi, Professor of Radiology, Jikeikai Medical School, Tokyo, Japan

Jacob L. Marks, Fox River Tuberculosis Sanitarium, Chicago, Illinois, U.S.A.

Howard F. Root, Lecturer in Medicine, Harvard Medical School, Boston, Massachusetts, U.S.A.

Surgery, Chemotherapy and Radiation Therapy of Lung Tumors

Donato G. Alarcon, Professor of Clinical Medicine, University of Mexico, Mexico City, Mexico

Fortunato S. Guerrero, Professor of Surgery, University of Santo Tomas, Pasay City, Philippines

Kiyoshi Inada, Instructor in Surgery, Okayama University Medical School, Okayama, Japan

Juan S. Netto, Asuncion, Paraguay

Henry J. Stanford, Thoracic Surgeon, Tucson Medical Center, Tucson, Arizona

Kempo Tsukamoto, Tokyo, Japan

Bronchoesophagology

Arthur G. Falls, President, Medical Staff and Senior Attending Surgeon, Provident Hospital, Chicago, Illinois, U.S.A.

Joseph E. Ferkany, Kula Sanatorium, Waiakoa, Maui, Hawaii

Paul H. Holinger, Professor of Bronchoesophagology, University of Illinois College of Medicine, Chicago, Illinois, U.S.A.

Chevalier L. Jackson, Professor of Laryngology and Bronchoesophagology, Temple University School of Medicine, Philadelphia, Pennsylvania, U.S.A.

Jo Ono, Professor of Bronchoesophagology, Keio University Medical School, Tokyo, Japan

M. A. Pollock, Pollock Clinic, Toronto, Ontario, Canada

Philip Strax, Director of Radiology, Elmhurst General Hospital, New York, U.S.A.

Kaoru Yamamoto, Professor of Bronchoesophagology, Osaka Municipal University Medical School, Osaka, Japan

Management of the Coronary Patient

John F. Briggs, Associate Clinical Professor of Medicine, University of Minnesota Medical School, St. Paul, Minnesota, U.S.A.

Kenzo Oshima, Professor of Internal Medicine, Nihon University Medical College, Tokyo, Japan

Nicholas Tsamboulas, Professor of Medicine, University of Athens, Athens, Greece

Congestive Heart Failure

Joseph F. Borg, Assistant Clinical Professor of Medicine, University of Minnesota Medical School, St. Paul, Minnesota, U.S.A.

Harvey L. Daiell, Director, Scientific Department, Lakeside Laboratories, Milwaukee, Wisconsin, U.S.A.

Albert L. Maisel, President, Bernalilli County Indian Hospital, Albuquerque, New Mexico, U.S.A.

Yanosuke Sagawa, Kyoto, Japan

Junichi Wakisaka, Kurume, Japan

Surgery of the Coronary Artery and Others

- Bomy R. Billimoria, Honorary Thoracic Surgeon, St. George's and Masina Hospitals, Bombay, India
Franklin R. Smith, Clinical Associate, Department of Surgery, University of Washington School of Medicine, Seattle, Washington, U.S.A.
Arthur E. Strauss, Assistant Clinical Professor of Clinical Medicine, Emeritus, Washington University Medical School, St. Louis, Missouri, U.S.A.
Saburo Sugie, Tokyo, Japan

Fungus Infections

- Orin J. Farness, Tucson Medical Center, Tucson, Arizona, U.S.A.
Ladislao Pollak, Chief, Diagnosis Section, Department of Bacteriology, Instituto Nacional de Tuberculosis, Caracas, Venezuela
Henry C. Sweany, Director of Research, Pathology and Allied Sciences, Missouri State Sanatorium, Mt. Vernon, Missouri, U.S.A.

Chemotherapy of Tuberculosis

- Manuel Albertal, Director, Sanatorio Albertal, Buenos Aires, Argentina
Shinnosuke Fujita, Chief, Tuberculosis Division, Tokyo Communications Hospital, Tokyo, Japan
Yoshimitsu Fukuhara, Department of Clinical Research, Institute for Infectious Diseases, University of Tokyo Medical School, Tokyo, Japan
Jiro Gomi, Assistant Professor of Medicine, Keio University School of Medicine, Tokyo, Japan
Fumio Ito, Doonoma Medical Clinic, Osaka University Hospital, Osaka, Japan
Yuzo Kawamori, Professor of Medicine, Kumamoto University School of Medicine, Kumamoto, Japan
Osamu Kitamoto, Professor of Medicine, University of Tokyo Medical School, Tokyo, Japan
Miklos Lanyi, Assistant Professor and Chief, Laboratory Service, University Medical School, Budapest, Hungary
Jiro Mikami, Chief, Department of Pulmonary Disease, First Tokyo National Hospital, Tokyo, Japan
Masukazu Naito, Associate Professor, Tuberculosis Institute, Kyoto University, Kyoto, Japan
Charles K. Petter, Superintendent and Medical Director, Lake County Tuberculosis Sanatorium, Waukegan, Illinois, U.S.A.
David B. Rosenthal, Director of Tuberculosis, Department of Health, Melbourne, Australia
Shigeichi Sunahara, Director, Tokyo National Sanatorium, Tokyo, Japan
Kin Yamada, Chief, Department of Internal Medicine, Tokyo Jikeikai School of Medicine, Tokyo, Japan
A. Omodei Zorini, Director, Carlo Forlanini Institute, Rome, Italy

Surgery of Heart Valves

- Seiji Kimoto, Chief, Department of Surgery, Tokyo University Hospital, Tokyo, Japan
Yoshio Ozawa, Professor of Medicine, Osaka University Hospital, Osaka, Japan
Shigeru Sakakibara, Professor of Cardiovascular Surgery, Tokyo Women's Medical College, Tokyo, Japan
Rudolph T. Wagner, Adjunct Professor of Medicine, University of Miami School of Medicine, Miami Beach, Florida, U.S.A.
Helge B. Wulff, Professor of Surgery, Lund University, Malmö, Sweden

Asthma

- Takayoshi Misawa, Tokyo, Japan
Phillip H. Narodick, Clinical Instructor, University of Washington School of Medicine, Seattle, Washington, U.S.A.
Nathan E. Silbert, Chief of Allergy, Lawrence Quigley Memorial Hospital and Soldier's Home, Lynn, Massachusetts, U.S.A.
Hitohiko Sugiura, Tokyo, Japan
Masuichi Takino, Dai Nippon Zoki Institute for Medical Research, Osaka, Japan

BCG Vaccination and Chemoprophylaxis

- Yasuyuki Chiba, Medical Director, Health Control Department, National Railway and Tokyo Hospital, Tokyo, Japan
Erik J. Hedvall, Professor of Phthisiology, Uppsala University, Uppsala, Sweden
Katsumi Kaida, Professor and Chief, Research Institutes, Kyushu University Faculty of Medicine, Fukuoka, Japan
Iwao Kanno, Assistant Professor, Research Institute for Tuberculosis, Tohoku University, Sendai, Japan
Manuel Quisumbing, Sr., Visiting Physician, San Pablo City Hospital, San Pablo City, Philippines
S. Sen, First Physician, Tata Main Hospital, Jamshedpur, India
J. C. Tao, Medical Director, Provincial Taipei Tuberculosis Control Center, Taipei, Taiwan

Cor Pulmonale

Burgess L. Gordon, Director of Education, Lovelace Foundation, Albuquerque, New Mexico, U.S.A.
Tetsuo Jo, Director, National Sanatorium, Osaka, Japan
Frederick M. Lindauer, Clinical Instructor, Stritch Medical School, Loyola University, Chicago, Illinois, U.S.A.
Shinobu Miyamoto, Professor of Surgery, Nihon University Medical School, Tokyo, Japan
Hiroshi Sasamoto, Associate Professor of Medicine, Keio University, Tokyo, Japan
Hideo Ueda, Professor of Internal Medicine, Kikeikai Medical School, Tokyo, Japan

Use of Steroids in Pulmonary Diseases

Celso de los Angeles, Quezon Institute, Quezon City, Philippines
Naoyoshi Hayashi, Professor of Internal Medicine, Jikeikai School of Medicine, Tokyo, Japan
P. Kenzo Shinohara, Chief, Sakuramachi Hospital, Tokyo, Japan
Tzhihiro Takahashi, Chief of Clinical Pathology and Research, Hospital of Kitasato Institute, Tokyo, Japan
Hisashi Yoshida, Tokyo, Japan

Tuberculosis in Infants and Children

Angel R. de Leon, Iloilo Tuberculosis Pavilion, Iloilo City, Philippines
Carl H. Gellenthien, Medical Director, Valmora Sanatorium, Valmora, New Mexico, U.S.A.
C. T. Hsing, Chief, Tuberculosis Department, Veterans General Hospital, Taipei, Taiwan
Eva Mannheim, Sanatorio Nacional, Tegucigalpa, Honduras
Rafael J. Mejia C., Medical Director, Hospital-Sanatorio "La Maria," Medellin, Colombia
Sutemi Oka, Professor of Medicine, Tohoku University School of Medicine, Sendai, Japan

Occupational Diseases of the Chest

Ovidio Garcia-Rosell, Professor of Phthysiology, University of San Marcos, Lima, Peru
Jethro Gough, Professor of Pathology, Welsh National School of Medicine, Cardiff, Wales
H. W. Knipping, Medical Director, University Clinic, University of Cologne, Cologne, Germany
C. J. B. Muller, Head, Department of Radiology, Karl Bremer Hospital and University of Stellenbosch Medical Faculty, Cape Town, South Africa
Harry E. Tebrock, Assistant Clinical Professor of Industrial Medicine, New York University Bellevue Institute of Industrial Health, New York, New York, U.S.A.
Raman Viswanathan, Director, Patel Chest Institute, University of Delhi, Delhi, India
Sunao Wada, Chief, Ondo Sanatorium, Hiroshima, Japan

Clinical Pulmonary Physiology, Function Tests (Present Status)

Pan Chortis, Director, Sanatorium Sotiria, Athens, Greece
Joseph C. Massee, Associate Professor of Clinical Medicine, Emory University School of Medicine, Atlanta, Georgia, U.S.A.
Katsuyuki Kubo, Assistant Professor of Thoracic Surgery, Mie Prefectural University Hospital, Mie, Japan

Tuberculosis in the Aged

Carl C. Aven, Assistant Professor of Medicine, Emory University School of Medicine, Atlanta, Georgia, U.S.A.
J. E. J. Harris, Director, Student Health, University of New Mexico, Albuquerque, New Mexico, U.S.A.
Jun Nagasawa, Lecturer, Gunma University School of Medicine, Tokyo, Japan
William C. Voorsanger, Emeritus Chief of Medicine and Chest Diseases, Mt. Zion Hospital, San Francisco, California, U.S.A.

Tuberculoma

Bashir A. Akhtar, Consulting Physician, Modern Clinic, Karachi, Pakistan
Jorge A. Higgins, Guayaquil, Ecuador
Carmelo P. Jacinto, Radiologist, Quezon Institute, Manila, Philippines
Ichiro Oseki, Chief, Chest Clinic, Official Hospital of Nagoya City, Nagoya, Japan
Ushio Takahashi, Tuberculosis Institute, Kyoto University, Kyoto, Japan
Takashi Teramatsu, Tuberculosis Institute, Kyoto University, Kyoto, Japan
Hirotake Tokugawa, Lecturer, Keio University, Tokyo, Japan
Ruth W. Wilson, Clinic Chief, State Tuberculosis Clinic, Rochester, Pennsylvania
Toshio Yamamoto, Assistant Professor of Thoracic Surgery, Mie Prefectural University, Mie, Japan

Drug-Resistant Tubercle Bacilli

Frederick L. Giles, Honolulu, Hawaii
Susumu Hibino, Professor, Nagoya University School of Medicine, Nagoya, Japan
Mitsuo Hori, Osaka, Japan
Nobuhiko Katsunuma, Nagoya, Japan
Carlos G. Santiago, Jr., Notre Dame Hospital, Baguio City, Philippines
Shinichi Tanaka, Professor, Department of Biochemistry, Nagoya University
College of Medicine, Nagoya, Japan
Daizo Ushiba, Tokyo, Japan
Irving Willner, Director of Chest Disease, Department of Health, Newark, New
Jersey, U.S.A.

Artificial Heart-Lung Machine

Thomas G. Baffes, Department of Surgery, Northwestern University Medical
School, Chicago, Illinois, U.S.A.
Itsuro Fukukei, Nagoya, Japan
Benjamin M. Gasul, Director, Pediatric Cardiophysiology Departments, Cook
County Children's Hospital, Chicago, Illinois, U.S.A.
Takeshi Inoue, Tokyo, Japan
Hisao Manabe, Chief of Cardiovascular Surgery, Osaka University Medical
School, Osaka, Japan
Hideo Orihata, Tokyo, Japan
Kazumi Taguchi, Okayama University Hospital, Okayama, Japan

Treatment of Far-Advanced Tuberculosis

Harukata Baba, Nakana National Sanatorium, Tokyo, Japan
Otto L. Bettag, Director of Public Welfare, State of Illinois, Chicago, Illinois
Clara R. Gross, Associate Professor of Clinical Medicine, College of Physicians
and Surgeons, Columbia University, New York, New York, U.S.A.
Yoshio Hayashi, Assistant Professor of Otolaryngology, Keio University School
of Medicine, Tokyo, Japan
Kiho Kim, Chief, Chest Clinic, Severance University Hospital, Seoul, Korea
Shinobu Miyamoto, Professor of Surgery, Nihon University Medical School, Tokyo,
Japan
Chuzo Nagaishi, Director, Surgical Division, Tuberculosis Research Institute,
Kyoto University, Kyoto, Japan
Tasuku Nakada, Sendai, Japan
Susumu Nukada, President, Toho University, Tokyo, Japan
Chigashi Suzuki, Professor and Chief Surgeon, Research Institute for Tubercu-
losis and Leprosy, Sendai, Japan

Follow-up Results of Surgical Treatment of Pulmonary Tuberculosis

Ichiro Akakura, Professor of Surgery, Keio University School of Medicine,
Tokyo, Japan
Charles E. Hamilton, Associate Clinical Professor, State University of New York,
Brooklyn, New York, U.S.A.
Masaru Ono, Tokyo, Japan
Hirotugu Sawazaki, Head, Tuberculosis Department, Kanto Teishin Hospital,
Tokyo, Japan
Kazuo Sekiguchi, Thoracic Surgeon, Seirei Hospital, Hamamatsu, Japan
T. E. A. von Dedenroth, Tucson, Arizona, U.S.A.
Yoichi Yatsuka, Ube, Japan

X-ray Diagnosis and Radiation Hazards

Hideyuki Haruna, Professor of Radiology, Keio University School of Medicine,
Tokyo, Japan
Hans M. Landecker, Honorary Chest Physician, Chest Clinic, Sydney, Australia
Yasaburo Oike, Professor of Medicine, Hirotsuki University Medical Clinic,
Hirotsuki, Japan
Junjiro Okanishi, Director, Tokyo Fuchu Hospital, Tokyo, Japan
Coleman B. Rabin, Assistant Clinical Professor of Medicine, Columbia University,
New York, New York, U.S.A.
Abraham F. Schottlander, Faculty of Medicine, Rosario, Argentina
Fumiyo Shimazu, Professor of Radiology, Women's Medical College, Tokyo, Japan
Hiroshi Tachiiri, Professor of Radiology, Osaka University School of Medicine,
Osaka, Japan
Masao Tamaki, Professor, Nagasaki University Medical School, Nagasaki, Japan
Masao Tsuzuki, Director, Japanese Red Cross Hospital, Tokyo, Japan

Viral Infections of Respiratory Organs

Bruce L. Canada, Captain, M.C., Senior Medical Officer, U. S. Naval Station Hos-
pital, Subic Bay, Philippines
Ryoichi Fujii, Tokyo, Japan

Toshio Goto, Director and Chief, Sagami-hara National Hospital, Tokyo, Japan
Osamu Kitamoto, Medical Director, Institute for Infectious Diseases, Tokyo, Japan
S. H. Lawrence, Department of Infectious Diseases, University of California at Los Angeles, San Fernando, California, U.S.A.
Kenji Nakamura, Tokyo, Japan
Isao Tateno, Tokyo, Japan

Tubercle Bacilli and Tuberculin

Arao Imamura, Emeritus Professor, Faculty of Medicine, Osaka University, Osaka, Japan
Ryuzo Iwatsuru, Professor and Director, First Medical Clinic, Wakayama Medical College, Wakayama, Japan
Isaku Kasuya, Professor of Biochemistry, St. Paul University, Tokyo, Japan
Kiyoshi Konno, Sendai, Japan
Jay Arthur Myers, Professor of Internal Medicine and Public Health, Medical and Graduate Schools, University of Minnesota, Minneapolis, Minnesota, U.S.A.
Yoshio Takahashi, Sapporo, Japan

The scientific sessions of the Congress will be held in the Daiichi Building which has two theaters seating 700 and 300 persons, respectively. There will be simultaneous translation of the scientific papers into the official languages of the Congress. The Daiichi Building is centrally located and within walking distance of the Imperial and other hotels in downtown Tokyo. Arrangements are also being made for motion picture sessions and technical and commercial exhibits.

Inaugural Session

The Inaugural Session of the Congress will be held in the Yomiuri Hall on Sunday evening, September 7. Representatives of the Japanese Government, dignitaries representing the embassies and consulates of other countries, and prominent scientists from the various medical schools in Japan will be present for this important ceremony which will officially open the Congress. Many officials of the American College of Chest Physicians from countries throughout the world will also be present. Certificates of Fellowship will be awarded to new members of the College at the Inaugural Session.

The International College Medal for meritorious achievement in diseases of the chest will be presented by the President of the College to a renowned scientist.

Congress Banquet

The Congress Banquet will be held on Wednesday evening, September 10, at the Tokyo Kaikan, where there will be music, dancing and entertainment.

Social Activities

An interesting program of social activities is being planned by the committee in Japan, including official receptions, tea ceremonies served by Geisha girls, a Japanese kimono fashion show, flower arrangements, a Japanese musical, and special Japanese dining which will include tempura, Ghengis Khan, sukiyaki, etc. In addition, there will be tours to Mount Fuji, Shrines, Buddhas, Japanese gardens and parks, as well as other places of interest.

Executive Sessions

The Council on International Affairs of the College will hold two executive sessions during the Fifth International Congress. The first session will be held on Sunday afternoon, September 7, and the closing session on Thursday, September 11. The exact time and place of these meetings will be announced at a later date. The executive sessions are sponsored by the Council on International Affairs and are open to the Regents, Governors and Chapter Officials of the College throughout the world. Reports of the Councils on Pan American Affairs, European Affairs, Pan Pacific Affairs and African and Eastern Affairs, which serve under the Council on International Affairs of the College, will be presented. The Committee on Nominations will present the names of Regents and Governors to be elected for the term 1958-1960. The national flags of countries which have not yet been presented for display at the International Headquarters of the College in Chicago will be received at the closing executive session.

Committee Meetings

The following international committees have been organized and will hold their first biennial meeting in Tokyo during the Congress. All of the committees will meet on Saturday, September 6, at a time and place to be announced in the near future. College members who plan to attend the Congress in Tokyo are invited to attend the committee meetings which may be of special interest to them. It is requested that those who wish to attend the committee meetings please notify the Executive Offices of the College in Chicago as soon as possible in order that arrangements may be made for them to participate in the meetings of their choice.

INTERNATIONAL COMMITTEES

Undergraduate Medical Education
 Postgraduate Medical Education
 Chemotherapy and Antibiotics
 Non-Surgical Therapy
 Pulmonary Surgery
 Bronchoesophagology
 Physioologic Therapy
 Microbiology
 Pulmonary Diseases in Children
 Allergy
 Occupational Diseases of the Chest
 Psychosomatic Aspects of Diseases of the Chest

Chest Diseases in Institutions
 Chest Roentgenology
 BCG
 Tuberculin Testing
 Rehabilitation in Pulmonary Disease
 Clinical Cardiovascular Disease
 Electrocardiography
 Cardiovascular Physiology
 Hypertension
 Angiocardiography
 Pediatric Cardiology
 Cardiovascular Surgery
 Rehabilitation in Cardiovascular Disease

Officers of the Congress

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Prof. Taizo Kumagai

Vice-Presidents:

Prof. Hiroshige Shiota
Prof. Yoneji Miyagawa
Prof. Seizo Katsunuma
Prof. Arai Imamura
Prof. Yas Kuno

Executive Officers:

Prof. Masanaka Terada
Prof. Osamu Kitamoto
Prof. Masao Tsuzuki
Prof. Naotsugu Kawai

Secretary General:

Prof. Jo Ono

Chairman, Financial Committee:

Taizo Ishizaka

Chairman, Council on International Affairs:

Prof. Andrew L. Banyai, Milwaukee, Wisconsin, U.S.A.

Executive Director:

Murray Kornfeld, Chicago, Illinois, U.S.A.

Registration

The Registration Desk at the Congress will open on Saturday, September 6, in the Daiichi Building.

The Registration Fees for attendance at the Fifth International Congress are \$25.00 (U.S. Currency) for physicians and \$10.00 (U.S. Currency) for ladies, and other guests. Registration fees may be forwarded to any one of the following official banks for the Congress, with notification to Dr. Jo Ono, Secretary General, C.P.O. Box 553, Tokyo, Japan:

The Bank of Tokyo Ltd., Tokyo Office, Tokyo
 The Mitsui Bank Ltd., Head Office, Tokyo
 The Mitsubishi Bank Ltd., Head Office, Tokyo
 The Fuji Bank Ltd., Head Office, Tokyo
 The Daiichi Bank Ltd., Head Office, Tokyo
 The Sumitomo Bank Ltd., Tokyo Branch, Tokyo
 The Sanwa Bank Ltd., Tokyo Branch, Tokyo

Hotel Reservations

A sufficient number of rooms have been engaged at the leading hotels in Tokyo to accommodate those who wish to attend the Congress. All hotel reservations for the Congress must be made through the Cartan Travel Bureau, Inc., 108 North State Street, Chicago, Illinois, U.S.A. Doctors attending the Congress should specify the type of accommodations required, as well as arrival and departure dates.

Seventh International Congress on Bronchoesophagology

The Seventh Congress of the International Bronchoesophagological Society will be held in Kyoto, Japan, September 12-14, 1958, immediately following the fifth International Congress on Diseases of the Chest in Tokyo. A number of prominent physicians will participate in the scientific program at the Kyoto meeting. A group of physicians and their families attending the Tokyo Congress will travel together to Kyoto on September 12. For registration and further information about the International Congress on Bronchoesophagology, please address Dr. Chevalier L. Jackson, 3401 North Broad Street, Philadelphia, Pennsylvania, U.S.A.

MEDICAL SERVICE BUREAU

POSITIONS WANTED

Chest physician, F.C.C.P., age 43, 16 years experience (staff physician, consultant, medical director) graduate Class A university, licensed Illinois, Michigan, seeks position in chest hospital. Please address inquiries to Box 298B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

F.C.C.P., 47, married, desires to relocate. 3 years accredited residency in chest diseases and chest surgery, 15 years private practice. Considerable administration and industrial experience. Very extensive experience in bronchosophagology and other diagnostic techniques. Licensed in California. Seeking position in active chest disease department or tuberculosis control program. Please forward inquiries to Box 300B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

POSITIONS AVAILABLE

Two physicians wanted for approved residency in tuberculosis and pulmonary diseases. 200-bed hospital, integral part of medical school and of the primary general teaching hospital. Residency includes 3 months elective training in related fields such as cardiopulmonary laboratory, research bacteriology laboratory, infectious diseases. Salary \$225 month minimum. Write: Woodlawn Hospital, 3819 Maple Avenue, Dallas, Texas.

Physician interested in pulmonary diseases wanted for 170-bed state supported tuberculosis hospital established 2 years. Active surgical program, outpatient service, x-ray and laboratory. Consultants in all branches. U. S. citizenship and Alabama medical license or eligibility required. Salary \$8500-\$9500 depending on qualifications. Quarters to be made available. Apply: Medical Director, Sixth District Tuberculosis Hospital, 800 St. Anthony Street, Mobile, Alabama.

Recruitment of physicians, full-time, TB-NP Service, Los Angeles area. Hospital is affiliated with 3 medical schools. Salary \$8990 through \$11,395 plus 25% specialty allowance. Contact Manager, VA Hospital, Sepulveda, California.

Qualified tuberculosis and chest physician wanted, 45 years or under, licensure and citizenship required. Hospital fully accredited by Joint Commission. Medical and surgical tuberculosis programs. Community 50,000 population. Civil service, state retirement, social security plan. Excellent starting salary. \$85 monthly deduction beautiful furnished home. Duties—ward physician, assistant medical director, assistant superintendent. Apply: Superintendent, Oregon State Tuberculosis Hospital, Salem, Oregon.

Physician wanted for approved residency in tuberculosis. Starting salary \$600 monthly, includes furnished modern home. Must be eligible for California licensure. Write: Medical Director, Tulare-Kings Counties Hospital, Springville, California.

Assistant medical director wanted. California license, previous experience in chest diseases, prefer married man with U. S. citizenship. Salary \$750 monthly, includes furnished modern house; promising future. Accredited bi-county hospital, 219 beds pulmonary diseases, 30 beds rehabilitation chronic illness. Write: Medical Director, Tulare-Kings Counties Hospital, Springville, California.

Immediate opening for fellow in pediatric pulmonary diseases. Pediatric residency in approved hospital required. Salary \$5000 per year. Affiliation with Baylor University Medical School. Send personal qualifications to Dr. Katharine Hsu, 3602 West Dallas Street, Houston 19, Texas.

CALENDAR OF EVENTS

NATIONAL AND INTERNATIONAL MEETINGS

24th Annual Meeting, American College of Chest Physicians
Fairmont Hotel, San Francisco, June 18-22, 1958

Fifth International Congress on Diseases of the Chest

Council on International Affairs
American College of Chest Physicians
Tokyo, Japan, September 7-11, 1958



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3

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